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## DUODENOGASTRIC INTUSSUSCEPTION

### AN EXPERIMENTAL STUDY OF PEPTIC ULCER

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The cause of peptic ulcer is unknown, and, unlike many diseases, even its control on empirical grounds is unsatisfactory. The amount of clinical and experimental work that has been done on the subject is enormous, and, as may be expected, there is a wide difference of opinion concerning its many phases. It is impossible to review all of the prevailing ideas adequately in this short paper; however, a brief summary of current opinion is important in order to lay the foundation for successful study.

From the standpoint of the clinician and the experimental surgeon, three theories have been advanced as to the cause of peptic ulcer: first, the physiologic or secretory theory; second, the local anatomic or mechanical theory, and third, the general constitutional or systemic theory.

The secretory theory, or the theory based on the digestive action of the gastric juice and the normal resisting powers of gastric and duodenal mucous membrane, has been carefully and extensively studied by Mann and Williamson,<sup>1</sup> Matthews and Dragstedt<sup>2</sup> and many others. Practically all experimental and clinical observers record the altered gastric juice as the one great outstanding cause. Whether the increased acidity is merely quantitative or is due to an increase in hydrogen ion concentration is not entirely clear. Whether the ulcer precedes or follows this increase is also an unsettled point. One fact is agreed on, and that is that peptic ulcer and hyperacidity go hand in hand.

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From the Department of Surgery and Experimental Surgery, Indiana University School of Medicine.

This work was made possible by a grant from the Landon Research Fund and the Eli Lilly Research Fellowship.

1. Mann, F. C. and Williamson, C. S.: The Experimental Production of Peptic Ulcer, *Ann. Surg.* **77**:409, 1923.

2. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, *Surg., Gynec. & Obst.* **55**:265 (Sept.) 1932.

The causes considered in the mechanical theory include, first, trauma, either vascular or direct injury to the part by foreign bodies, or rarely trauma produced by diaphragmatic hernia. The vascular disturbances mentioned include functional spasm of the arterioles and capillaries or organic lesions, such as embolism or thrombosis. It is said by some that a localized area of infarction may occur as a result of septic emboli from a symptomless focus of infection. This has not been adequately proved<sup>3</sup> and is therefore not accepted by many observers. On the contrary, most ulcers begin in the mucosa and erode outward. Pylorospasm is said to be an important mechanical factor because regurgitation of the neutralizing duodenal contents cannot take place as it normally does.

Lastly, the general health of the patient and particularly the condition of his nervous system have given rise to the so-called neurogenic theory of ulcer. Cushing<sup>4</sup> has shown that tumor of the brain and peptic ulcer occur together frequently enough for their simultaneous presence to be more than a coincidence. That a constitutional type for ulcer exists seems to have been clearly brought out by Pende<sup>5</sup> and by Draper<sup>6</sup> in their excellent studies. Some have classified peptic ulcer as of trophic origin. Obviously, these are clinical rather than experimental observations.

#### PURPOSE OF OUR EXPERIMENTS

The philosophy underlying our work is based on the hypothesis that since peptic ulcer practically always occurs in the pyloric end of the stomach and the first portion of the duodenum, some local factor must be the underlying cause. This area is a *locus minoris resistentiae* and is subject to the same laws of pathology that apply elsewhere in the body, augmented no doubt by constitutional factors which certainly play a rôle in this decrease in local resistance. In attempting to define this process accurately and to identify its component parts, one must first study the normal anatomy and physiology. In making such an analysis one must not upset normal relationships any more than is absolutely necessary for the experiment. A criticism of many investigations has been justly made that the abnormal or pathologic deviation is actually introduced by the experiments themselves. After the normal physiologic relationships have been ascertained, the pathologic process found in peptic ulcer may be reproduced, again with as little alteration of the part as possible. Finally, the way to prevention and cure may be discovered in the light of accurate observation.

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3. Berman, J. K.: Critical Evaluation and Present Status of the Theory of Chronic Focal Infection, *J. Indiana M. A.* **24**:665, 1931.

4. Cushing, Harvey: Peptic Ulcers and Interbrain (Balfour Lecture), *Surg., Gynec. & Obst.* **55**:1 (July) 1932.

5. Pende, Nicola: Constitutional Inadequacies, Philadelphia, Lea & Febiger, 1928.

6. Draper, George: Disease and the Man, New York, The Macmillan Company, 1930.

Anatomically and physiologically, the pyloric antrum and the first portion of the duodenum have one chief characteristic in common, that is, alkaline mucin-secreting glands—the pyloric glands in the former and Brunner's glands in the mucous and submucous coats of the latter. The fact that there are no plicae circulares (valvulae conniventes) in the pars superior duodeni and much lymphoid tissue has also been noted. The rôle of the pyloric sphincter has been studied by many observers. Recently, Gianturco<sup>7</sup> found that the pylorus responds to approaching waves of peristalsis much as does the adjacent part of the pars pylorica and that relaxation of the pylorus alone is not followed by passage of food, which takes place only when the pylorus and the duodenum are relaxed at the same time. This may be seen fluoroscopically in the experiments to be described, and the peristaltic wave carries through the area operated on, permitting barium sulfate to go easily into the duodenum.

1

#### PRODUCTION OF DUODENAL INTUSSUSCEPTION INTO THE STOMACH

Since ulcer and acid are so closely interrelated, we wished to learn what might happen if the ulcer-bearing area were brought up into the more acid prepyloric portion of the stomach. In other words, we would seek to produce a living transplant of the pars superior duodeni in a new and more highly acid environment. If successful, we could observe the effect of this acidity on the mucosa and, in turn, the effect of duodenal mucous membrane on the physiology of the stomach.

*Material and Technic.*—On Oct. 30, Nov. 22 and Dec. 13, 1933, the first group of dogs were successfully operated on (nos. 938, 957 and 985). The technic employed is shown in figure 1, 1 to 8, inclusive. The effect of this procedure is to produce intussusception of the duodenum into the stomach (figs. 2 and 3). The dogs received 800 cc. of 3 per cent dextrose in physiologic solution of sodium chloride subcutaneously twice daily for from six to eight days following the operation. The first group of tests were done to determine the percentage of free and of combined acid. Three animals (938, 957 and 985) from the group subjected to operation and three controls (2, 20 and 983) were used.

*Gastric Analyses.*—An ordinary well lubricated Rehfuß stomach tube and a 30 cc. syringe were used to aspirate the material. Food was withheld for twenty-four hours previous to the experimental procedure. The dogs were then given 400 cc. of water by stomach tube and at the same time a subcutaneous injection of 0.1 mg. of histamine hydrochloride. Specimens were drawn one-half and one hour later. We collected from 20 to 50 cc. of the contents of the stomach from each animal for the analysis.

The specimens were centrifugated and filtered and 10 cc. of the substance was titrated in the usual manner for free, combined and total hydrochloric acid, Toepfer's reagent and phenolphthalein being used as indicators. Quantitative determina-

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7. Gianturco, Cesare: Experimental Studies on the Pyloric Mechanism, Proc. Staff Meet., Mayo Clin. 8:784 (Dec. 27) 1933.



tions for mucin were done by treating 1 cc. of the gastric filtrate with 0.5 cc. of normal sulfuric acid, autoclaving the filtrate for one hour at 15 pounds of pressure and then neutralizing it with 0.5 cc. of normal sodium hydroxide and 1 drop of phenolphthalein. The addition of a dilute solution of sodium carbonate turned the substance to pale pink. The mucin was treated according to the Folin colorimetric quantitative determination of blood sugar, and the results were calculated as such. In some of the animals that were operated on the mucus was so thick that we could not aspirate it. This may account for the great varia-

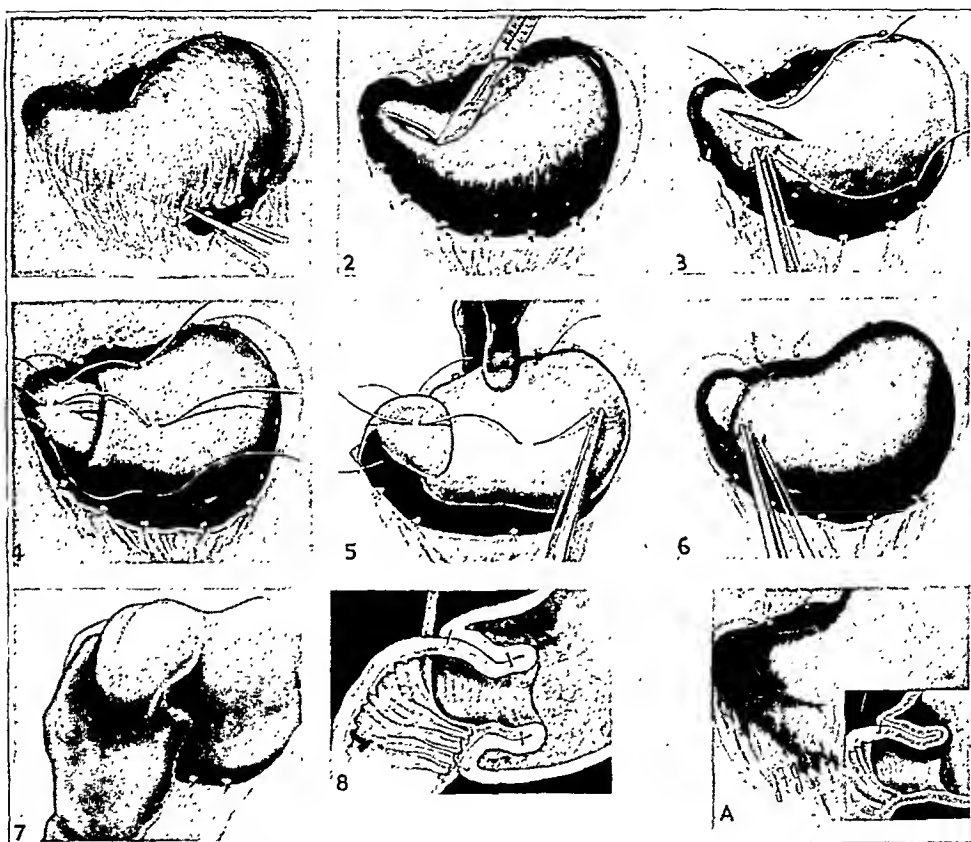


Fig. 1.—Photographs showing the technic for producing an intussusception of the duodenum into the stomach. In 1, the lesser and the greater curvature of the stomach are freed; in 2, the pyloric sphincter is divided in the manner of a Rammstedt pyloroplasty; in 3, interrupted Lembert silk sutures are introduced anteriorly and posteriorly, ending about half way between the pylorus and the common bile duct (proximal row of sutures); in 4, the second or distal row of sutures are shown ending just proximal to the common bile duct; in 5, the distal row of sutures are placed on the posterior wall of the stomach by rotating the greater curvatures upward; in 6, extra sutures are placed around the invagination completing the operation; in 7, the patency of the newly formed pyloric canal is tested, and in 8, a cross-section of the completed operation is depicted. The common bile duct and ampulla are shown in their new relationship. *A* shows the method of covering a perforated duodenal ulcer by using part of the anterior wall of the stomach. The inset is a cross-section of the same.

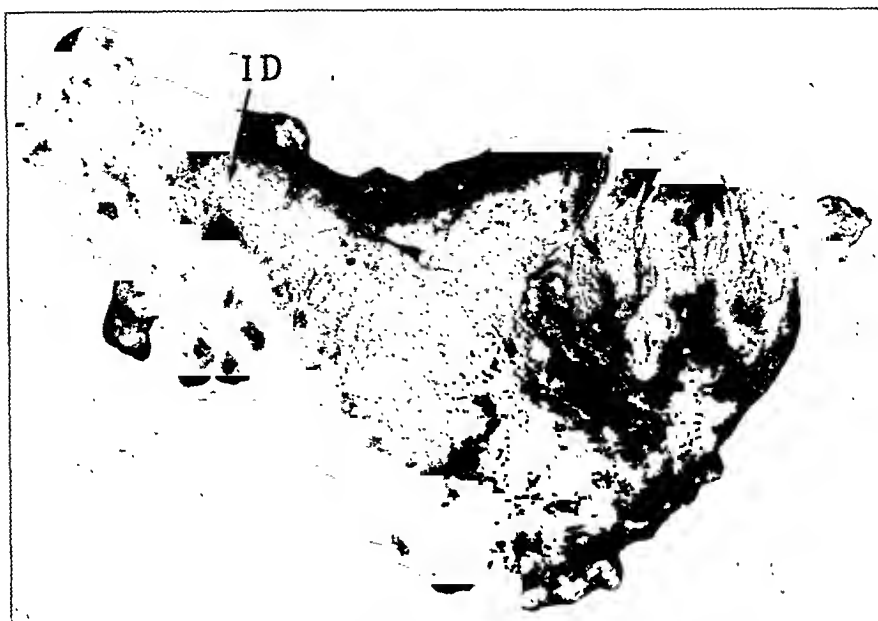


Fig. 2.—Posterior wall of the stomach and the duodenum, showing the duodenogastric intussusception seven months after operation. *ID* indicates the invaginated duodenum.

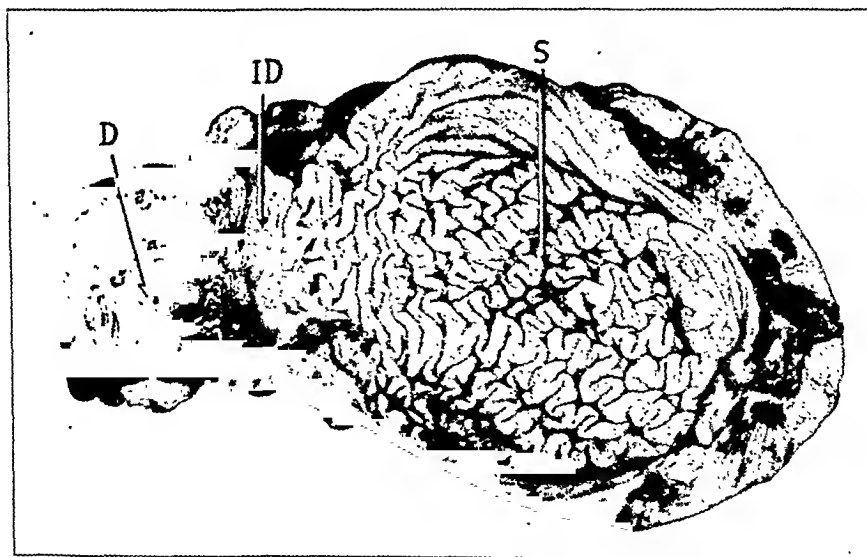


Fig. 3.—Interior of the stomach and the duodenum, showing duodenogastric intussusception nine months after operation. *ID* indicates the invaginated duodenum; *S*, the stomach, and *D*, the duodenum.

tion in the results. The laboratory work was done by the Central Laboratories of the Indiana University School of Medicine, which is a separate unit from the experimental division.

The determinations were repeated six times for each animal (tables 1, 2 and 3). General averages were computed by averaging the results of all tests made on all dogs. This revealed that the acid values of the dogs that were operated on were higher than the values for the normal dogs (table 3). Determinations of mucin were made also, but our readings were variable for this first group, owing in part to the use of small stomach tubes, through which it was impossible to aspirate all of the thick mucus. However, grossly long stringy ropes of mucus were removed after withdrawal of the stomach tube. These were much more profuse and thicker in the animals that were operated on than in the controls.

TABLE 1.—*Gastric Acid and Mucin Content of Control Animals*

	Date	One-Half Hour Sample			One Hour Sample		
		Free Hydro-chloric Acid, Percentage	Combined Acid, Percentage	Mucin, Mg. per 100 Cc.	Free Hydro-chloric Acid, Percentage	Combined Acid, Percentage	Mucin, Mg. per 100 Cc.
Animal 20	3/ 8/34	35	55	241.0	35	45	67.0
	3/16/34	25	35	0	45	50	10.8
	3/25/34	14	16	0	46	52	11.1
	3/30/34	35	45	42.0	45	55	38.0
	4/ 6/34	25	30	0	50	60	10.0
	4/13/34	26	36	65.0	44	52	37.0
Animal 2	3/ 8/34	30	36	0	30	45	0
	3/16/34	20	35	20.0	35	65	20.0
	3/25/34	10	16	10.0	36	42	19.0
	3/30/34	40	50	11.9	65	70	17.7
	4/ 6/34	60	85	61.4	40	95	100.0
	4/13/34	4	12	0	0	18	0
Animal 883	3/ 8/34	10	15	0	20	55	0
	3/16/34	4	8	26.6	8	23	0
	3/25/34	50	60	0	30	35	10.0
	3/30/34	30	35	0	35	40	0
	4/ 6/34	18	30	0	30	70	0
	4/13/34	18	22	0	18	26	13.3
Average		25.2	34.5	26.5	34	50.2	19.6

*Emptying Time.*—A study was next made of the emptying time of the stomach after our operation had been performed. This was compared with the emptying time of normal controls. We found it necessary to do the experiment several times before tabulating the results. This enabled the animals to adjust themselves and gave us more accurate data. In carrying out this study the work of Van Liere and Crisler<sup>8</sup> was reviewed. They found that the average emptying time was six and fifty-nine hundredths hours but that the normal extremes varied from five and forty-two hundredths to eight and seven hundredths hours. The meal used consisted of the following ingredients: hamburger, 40 Gm.; dried ground bread, 10 Gm.; milk, 50 cc., and barium sulfate, 15 Gm.

8. Van Liere, Edward J., and Crisler, George: *Proc. Soc. Exper. Biol. & Med.* **31**:85, 1933.

Each of the experimental animals was fed this meal at the same time on the days that examinations were made. In our first series roentgenograms were employed, but in the remainder of the six series the fluoroscope was used to ascertain the emptying time. Three controls (2, 20 and 983) and three animals that were operated on (938, 957 and 985) were used.

TABLE 2.—*Gastric Acid and Mucin Content in Animals That Were Operated On*

	Date	One-Half Hour Sample			One Hour Sample		
		Free Hydro- chloric Acid, Percentage	Combined Acid, Percentage	Mucin, Mg. per 100 Cc.	Free Hydro- chloric Acid, Percentage	Combined Acid, Percentage	Mucin, Mg. per 100 Cc.
Animal 938	3/ 8/34	30	35	0	70	80	40.0
	3/16/34	20	24	8.5	50	60	13.3
	3/25/34	30	35	0	20	80	36.0
	3/30/34	10	20	7.5	30	45	13.0
	4/ 6/34	25	35	80.0	50	60	10.5
	4/13/34	10	45	0	0	10	0
Animal 957	3/ 8/34	30	40	0	20	85	14.3
	3/16/34	24	32	8.5	42	48	10.9
	3/25/34	30	40	0	50	65	14.3
	3/30/34	5	10	0	35	56	0
	4/ 6/34	35	30	16.6	70	90	13.0
	4/13/34	14	32	0	50	87	0
Animal 985	3/ 8/34	60	70	12.1	75	90	22.8
	3/16/34	22	26	8.5	56	70	26.0
	3/25/34	55	65	12.8	75	90	21.0
	3/30/34	50	65	14.8	65	75	22.0
	4/6 34	50	55	10.0	60	65	14.8
	4/13/34	16	28	0	8	30	0
Average		28.6	38.1	9.9	50.3	65.9	15.1

TABLE 3.—*Average of the Six Gastric Analyses on all Animals\**

	One-Half Hour Sample			One Hour Sample		
	Free Hydro- chloric Acid, Percentage	Combined Acid, Percentage	Mucin, Mg. per 100 Cc.	Free Hydro- chloric Acid, Percentage	Combined Acid, Percentage	Mucin, Mg. per 100 Cc.
Animals operated on	28.6	38.1	9.9	50.3	65.9	15.1
Normal control animals	25.2	34.5	26.5	34.0	50.2	19.6

\* Great variation in the mucin content may be due in part to the difficulty of aspirating the thicker and more tenacious mucus through the small tubes. This was especially true in the animals that had been operated on.

The average emptying time was one hour. The emptying time was forty minutes faster in the animals with duodenogastric intussusception than in the normal controls (table 4).

*Effects of Operation on the Invaginated Duodenum.*—Dog 985 was killed after seven months and dog 938 after nine months in order to determine the ultimate organic effect of our operative procedure (fig. 2 and 3). Both animals were normal and in good health at the time they were killed. No gross changes were found either in the stomach or in the invaginated portion of the duodenum. Bile was present mixed with large quantities of mucus. Microscopic study revealed

some desquamation of the mucous membrane over the invaginated portion; however, Brunner's glands appeared to be normal in every way (fig. 4). Dr. Frank Forry of the pathology department of the university examined the sections carefully and found that there were no degenerative changes or other significant reactive phenomena in Brunner's glands in each of the several sections. The glands did not differ significantly in any way from those found in preparations from normal control animals.

*Comment.*—These experiments reveal that the presence of Brunner's glands in the stomach seems to cause an increase in the percentage of both free and combined acid. This increase is all the more conclusive because the increased emptying time and the presence of bile suggest an open pylorus, which should permit neutralization to some extent by the alkaline duodenal content and to a greater extent by the secretion of

TABLE 4.—*Summary of Emptying Time Revealed on Six Examinations\**

Animal	1	2	3	4	5	6
2 (control).....	7 hr., 30 min.	7 hr., 15 min.	7 hr., 30 min.	7 hr.	8 hr.	7 hr., 30 min.
20 (control).....	7 hr.	7 hr., 15 min.	7 hr., 15 min.	7 hr.	7 hr.	7 hr., 30 min.
983 (control).....	7 hr., 30 min.	7 hr.	8 hr.	7 hr., 30 min.	7 hr., 30 min.	6 hr., 45 min.
937 (operation)....	5 hr., 30 min.	4 hr., 46 min.	5 hr., 15 min.	5 hr.	5 hr., 30 min.	5 hr.
985 (operation)....	7 hr., 30 min.	5 hr., 5 min.	6 hr., 50 min.	5 hr., 45 min.	6 hr., 30 min.	6 hr., 15 min.
938 (operation)....	7 hr., 15 min.	4 hr., 25 min.	5 hr., 34 min.	5 hr., 50 min.	4 hr., 51 min.	5 hr., 10 min.

Average emptying time of normal control animals: 7 hr., 20 min.

Average emptying time of animals operated on: 5 hr., 40 min.

\* The report of the roentgen studies was submitted by Dr. Wright of the department of x-ray, Indiana University Hospitals.

Brunner's glands, which, according to Florey and Harding,<sup>9</sup> is alkaline to  $p_H$  8 plus. The gross increase in the quantity and quality of mucus seems to be due to the higher acid medium created. In other words, our experiments seem to show that Brunner's glands are stimulated to increased production of mucin by higher acid values and that these same glands in turn, owing to this stimulation, cause an increase in the hydrochloric acid of the stomach. Brunner's glands seem to have two functions: a local protective mucin-producing action and a hormonal acid-stimulating mechanism. Both functions have been separately observed by other investigators. Murray<sup>10</sup> found that when that part

9. Florey, H. W., and Harding, H. E.: The Functions of Brunner's Glands and the Pyloric End of the Stomach, *J. Path. & Bact.* **37**:431, 1933.

10. Murray, Margaret M.: The Small Intestine and Gastric Secretion, with Special Reference to Brunner's Glands, *J. Physiol.* **69**:48, 1930.

of the duodenum which contains Brunner's glands is made into an extract and injected into cats (normally insensitive to histamine) an increase in hydrochloric acid and pepsin results. This was not true when the mucous membranes of other portions of the gastro-intestinal tract were used. Florey and Harding<sup>9</sup> found that Brunner's glands produced an alkaline mucin with a  $p_H$  of 8, or equal to tenth-normal sodium bicarbonate. When hydrochloric acid was allowed to come into



Fig. 4.—Duodenogastric intussusception, showing the invaginated portion. *D* indicates the duodenum, and *S*, the stomach.

contact with the glands, there was an increase in the amount of mucin, which protects the normal pylorus and duodenum against the formation of ulcer. The second group of experiments described in this paper lend support to their hypothesis.

The increase in emptying time is to be expected because of the division of the pyloric sphincter. This procedure nullifies the effect of a possible pylorospasm as a cause of hyperacidity and again adds to

the contention that Brunner's glands have a "secretin" action. That the glands are actually living and functioning seems to be established by our microscopic studies of their morphology as compared with that of the glands in the controls. We could not expect to find ulcers on the invaginated portion of the duodenum. Matthews and Dragstedt<sup>2</sup> have shown that different organs as well as parts of the alimentary canal can be implanted in the normal stomach without resulting ulceration of the organ. But if the alkaline duodenal juices were prevented from

TABLE 5.—*Study of Gastric Acid and Mucin Content \**

	Animal	Date	One-Half Hour Sample			One Hour Sample		
			Free Hydrochloric Acid, Percentage	Combined Acid, Percentage	Mucin, Mg. per 100 Cc.	Free Hydrochloric Acid, Percentage	Combined Acid, Percentage	Mucin, Mg. per 100 Cc.
Duodenogastric intussusception	112	11/21/34	72.0	42.5	8.0	73.0	48.5	8.4
		11/26/34	27.0	31.5	106.7	31.9	54.0	97.5
		12/ 4/35	19.5	43.5	34.8	15.0	56.5	55.2
	106	11/21/34	7.5	3.7	0.0	10.0	5.5	0.0
		11/26/34	34.5	26.5	94.0	47.5	29.0	97.5
		12/ 4/34	36.5	72.0	83.5	40.0	69.5	88.8
	Average.....		32.5	36.6	54.5	36.2	43.8	57.5
Finney pyloroplasty	102	11/21/34	37.0	41.0	0.0	25.0	39.0	8.7
		11/26/34	46.7	8.3	14.5	75.0	4.5	22.2
		12/ 4/34	33.0	23.0	80.0	87.0	20.5	64.0
	Average.....		45.5	23.7	31.5	62.3	21.3	31.6
Control	134	11/21/34	18.0	25.0	0.0	10.0	22.2	0.0
		11/26/34	5.0	20.5	97.5	8.5	20.0	106.7
		12/ 4/34	47.5	47.2	36.4	37.8	20.0	0.0
	Average.....		23.5	30.9	44.6	18.7	20.7	35.5

\* The animal on which a Finney pyloroplasty was performed had the highest amount of free hydrochloric acid and the second highest combined acid content. Dogs operated on by our technic came next. The control had the lowest amount of free hydrochloric acid and about the same amount of combined acid as the dog on which a Finney operation was done. The animals used for duodenogastric intussusception had the highest amount of mucin, while the dog on which a Finney pyloroplasty was done had the lowest amount.

entering the stomach by a valve in the pylorus, the acids rose and ulcers developed. We have shown here that even in the presence of increased acids ulcers will not occur in the stomach or on the invaginated duodenum. However, the pylorus here remained open, allowing neutralization<sup>off</sup> by duodenal juices and protection by mucin from Brunner's glands.

#### PRODUCTION OF GASTRIC AND DUODENAL ULCERS IN EXPERIMENTAL AND CONTROL ANIMALS

Two more dogs (112 and 106) were operated on according to our technic. These, together with dog 957, operated on in November 1933, were the three animals studied after the administration of cinchophen. Another dog (102) was

operated on, and a Finney pyloroplasty was done. These dogs, with control 134, were studied for acids and mucin content as before (table 5). It was found that the dog in which the Finney pyloroplasty was done had the highest acidity, namely 22 per cent above that of the normal controls. The dogs operated on by our technic had an acidity that was 10 per cent higher than that of the normal controls. However, their mucin content exceeded that of the other dogs from 10 to 12 mg. Next the emptying time was determined. The emptying time in dog 102 (Finney pyloroplasty) was three and one-half hours faster than in the normal control. In dogs 112 and 106 (duodenogastric intussusception) it was about two hours faster than in the normal controls (table 6).

Our next step in this group of experiments was an attempt to produce typical peptic ulcer. This was accomplished by using cinchophen in toxic doses, as described by Van Wagoner and Churchill.<sup>11</sup> We administered 0.22 Gm. of

TABLE 6.—Emptying Time in Hours and Minutes at Three Examinations\*

Animal	Date	1	2	3
112 (operation).....	12/12/34	4 hr., 35 min.		
"	12/14/34	.....	5 hr., 20 min.	
	12/21/34	.....	.....	5 hr., 40 min.
103 (operation).....	12/12/34	4 hr., 17 min.		
	12/14/34	.....	5 hr., 50 min.	
	12/21/34	.....	.....	5 hr.
102 (Finney pyloroplasty).....	12/12/34	3 hr., 40 min.		
	12/14/34	.....	3 hr., 50 min.	
	12/21/34	.....	.....	Less than 4 hr.
134 (control).....	12/12/34	7 hr., 20 min.		
	12/14/34	.....	6 hr., 50 min.	
	12/21/34	.....	.....	7 hr., 30 min.

\* The fluoroscope was used to determine the emptying time, and the test meal employed was the same as that used in the previous experiments. The pyloric end of the stomach appeared more globular than normal, evidently because of the invagination of the first portion of the duodenum into the stomach; however, this part contracted along with the rest of the stomach as the peristaltic waves passed down (fig. 5). The emptying time of the dog on which a Finney pyloroplasty was done was less than four hours. The average emptying time in this group for animals with duodenogastric intussusception was five hours and twenty-four minutes, whereas the control required seven hours and thirteen minutes.

cinchophen per kilogram of body weight daily. The time required to produce the desired effect varied from three to eighteen days (average about ten days), depending on the size and resistance of the animals together with technical difficulties encountered in feedings. Careful postmortem studies were made after each experiment. The following descriptions of the gastro-intestinal changes were taken from the autopsy records.

Dog 983 (control).—Multiple gastric and duodenal erosions and several acute ulcers were found in the pylorus on the lesser curvature and also in the duodenum. One duodenal ulcer had perforated (fig. 6). Diffuse hemorrhagic colitis was also present.

11. Van Wagoner, F. H., and Churchill, T. P.: Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning: Preliminary Report, J. A. M. A. 99:1859 (Nov. 26) 1932; Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning in Dogs, Arch. Path. 14:860 (Dec.) 1932.



Dog 957 (duodenogastric intussusception).—Diffuse gastritis and duodenitis were present, but no ulcers were found in the stomach or duodenum. The lower part of the ileum and the entire colon contained numerous acute ulcers. An ulcer about 8 inches (20.3 cm.) above the ileocecal valve had perforated causing a fatal peritonitis.

Controls 101 and 134 together with dog 102 (Finney pyloroplasty) and dogs 112 and 164 (duodenogastric intussusception) were given cinchophen as described.

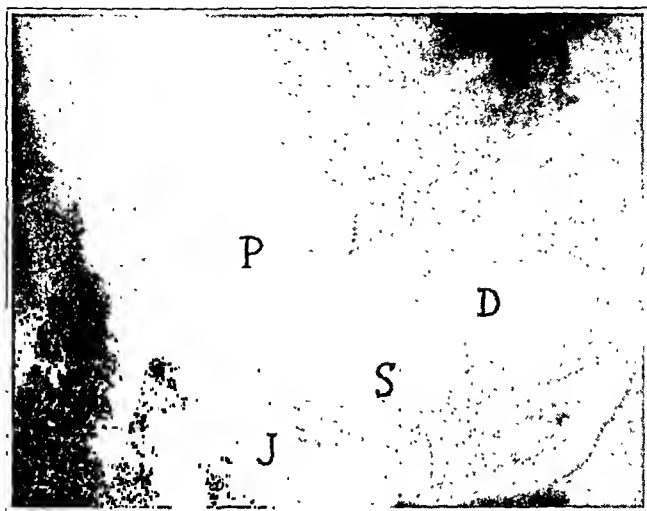


Fig. 5.—Roentgenogram showing the operative field. *S* indicates the stomach; *P*, the pylorus, showing the invaginated duodenum; *D*, the duodenum, and *J*, the jejunum.

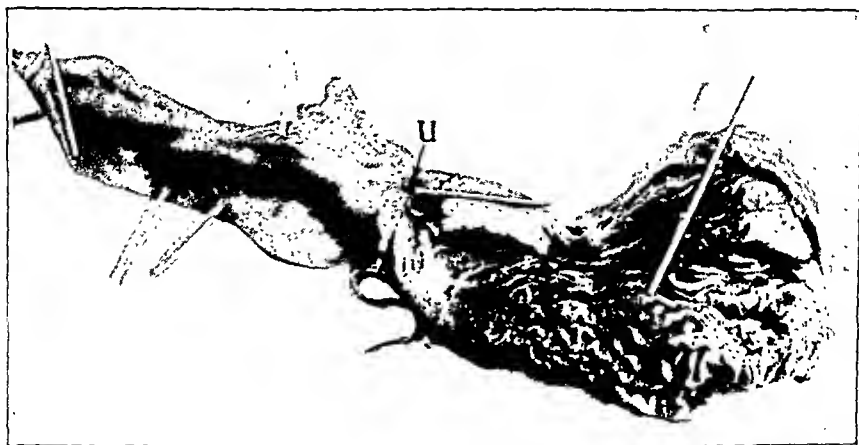


Fig. 6.—Multiple acute ulcers of the stomach and the duodenum in a normal control after toxic doses of cinchophen. *U* indicates a perforated ulcer of the duodenum.

The amounts of acid and mucin in the stomach were studied after the fourth day. There was a slight increase in the amount of acid and a greater increase in the amount of mucin in all dogs. The latter was especially true in animals with duodenogastric intussusception.

Dog 101 (control).—A diffuse hemorrhagic gastritis and duodenitis with acute gastric and duodenal ulceration were found. Many ulcerated areas, some very large, were seen in the mucous membrane of the small and large intestine.

Dog 134 (control).—For gastric studies before and after the feeding of cinchophen see tables 5 and 7, respectively. Acute gastric and duodenal ulcers were found.

Dog 102 (Finney pyloroplasty).—Several small acute ulcers were found in the pyloric end of the stomach and the first portion of the duodenum. One ulcer situated in the suture line had perforated. Diffuse enterocolitis was also present.

Dog 112 (duodenogastric intussusception).—Diffuse hemorrhagic enterocolitis was present. No gastric or duodenal ulcers were noted.

TABLE 7.—*Gastric Acid and Mucin Content Before and During the Administration of Toxic Doses of Cinchophen*

Date		Free Hydrochloric Acid, Percentage	Combined Acid, Percentage	Mucin, Mg. per 100 Cc.
Gastric Analysis of Normal Animal 134 During the Feeding of Cinchophen *				
1/ 1/35	½ hour.....	21.6	23.0	78.0
	1 hour.....	26.0	32.0	90.0
1/ 2/35	½ hour.....	16.7	22.0	65.0
	1 hour.....	20.0	21.0	80.0
1/ 4/35	½ hour.....	29.0	32.6	125.0
	1 hour.....	36.0	25.7	85.0
Gastric Analysis of Animal 164 Before the Administration of Cinchophen †				
2/20/35	½ hour.....	75.0	11.0	31.6
	1 hour.....	88.0	8.0	15.6
3/ 2/35	½ hour.....	10.0	40.0	13.2
	1 hour.....	68.0	13.5	10.2
3/ 8/35	½ hour.....	66.0	5.3	13.8
	1 hour.....	60.0	7.0	25.8
Gastric Analysis of Animal 164 During the Feeding of Cinchophen				
3/29/35	½ hour.....	44.6	20.2	26.6
	1 hour.....	59.5	35.5	25.5
3/30/35	½ hour.....	65.5	19.3	123.0
	1 hour.....	50.5	15.5	110.0
4/ 1/35	½ hour.....	67.2	40.2	113.4
	1 hour.....	68.0	36.7	106.6

\* Studies were made on the fourth, fifth and seventh days after the administration of cinchophen was begun. The gastric analysis of this animal before the administration of cinchophen is given in table 5.

† This animal was a healthy male and on Jan. 12, 1935, weighed 43 pounds (19.5 Kg.)

Four days after the feeding of cinchophen was started the free hydrochloric acid and the combined acid content were only slightly higher than before. However, there was a large increase in the amount of gastric mucin, which was extremely tenacious (table 7). Gastric studies were made on the fourth, fifth and seventh days after the administration of cinchophen in control 134. A greater rise in acid content occurred than in the animals operated on. The mucin content also rose, but it was not as high as in the dogs with the invaginated duodenum (tables 5 and 7).

Dog 102 (Finney pyloroplasty) had a perforation through the line of suture, although five months had elapsed since the operation was performed, which is ample time for complete healing. No ulcers of the stomach or duodenum were

found in dog 112 (duodenogastric intussusception), but a markedly hemorrhagic enterocolitis was present. The last animal studied was dog 164 (duodenogastric intussusception). The large upper and the small intestine showed the typical hemorrhagic mucosa previously described. There was little evidence of gastritis or duodenitis or gross ulceration in the stomach or duodenum proper; however, one large ulcer was seen on the invaginated portion (figs. 7 and 8).

*Comment.*—The cinchophen method of producing typical peptic ulcers does not alter the anatomy of the stomach or duodenum and is therefore excellent for experimental use. The repetition of previous studies on acids, mucin and emptying time served as a check on our results and added confirmatory evidence to previous deductions. We

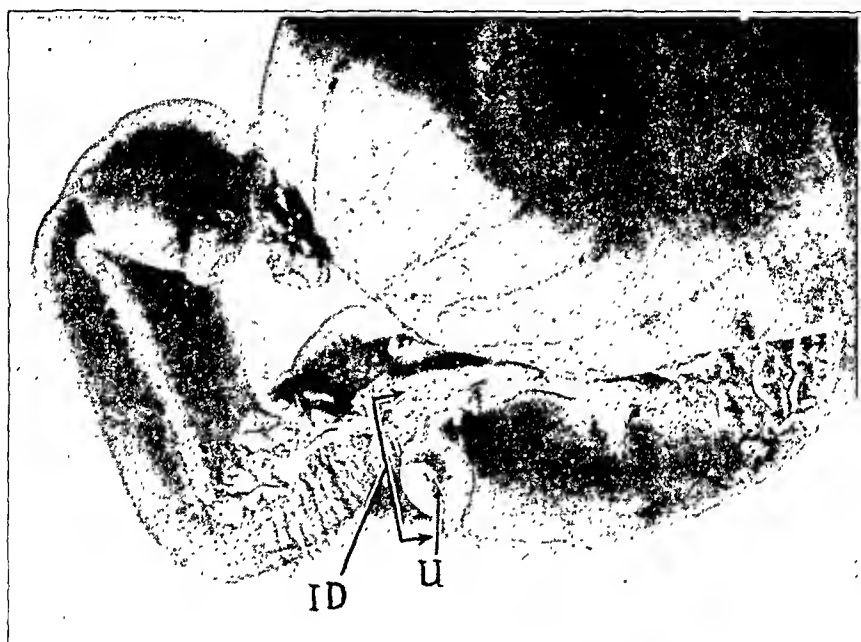


Fig. 7.—Interior of the stomach and the duodenum in an animal with duodenogastric intussusception after toxic doses of cinchophen. *ID* indicates the invaginated duodenum, and *U*, the ulcer.

were successful in producing typical acute peptic ulcers in normal dogs, in the dog on which a Finney pyloroplasty was done and in those subjected to duodenogastric intussusception. It will be noted that in the dog on which a Finney pyloroplasty was performed the acid content was higher than in the normal controls. We believe that this may be due to a closer proximity of Brunner's glands to the higher acid medium of the stomach, which starts the cycle of higher acidity and increased mucin content. The open pylorus and quick emptying time in this dog make this deduction more probable, for alkaline reflex was certainly amply present.

Only one of our dogs that was operated on had a peptic ulcer after the administration of cinchophen. This occurred without a significant rise in the acid content, as was true in all others so treated. We believe, therefore, that it is the absence of a sufficient amount of the protective influence of mucin rather than the increase in the amount of acids per se that is responsible for peptic ulcer. It is even possible that peptic

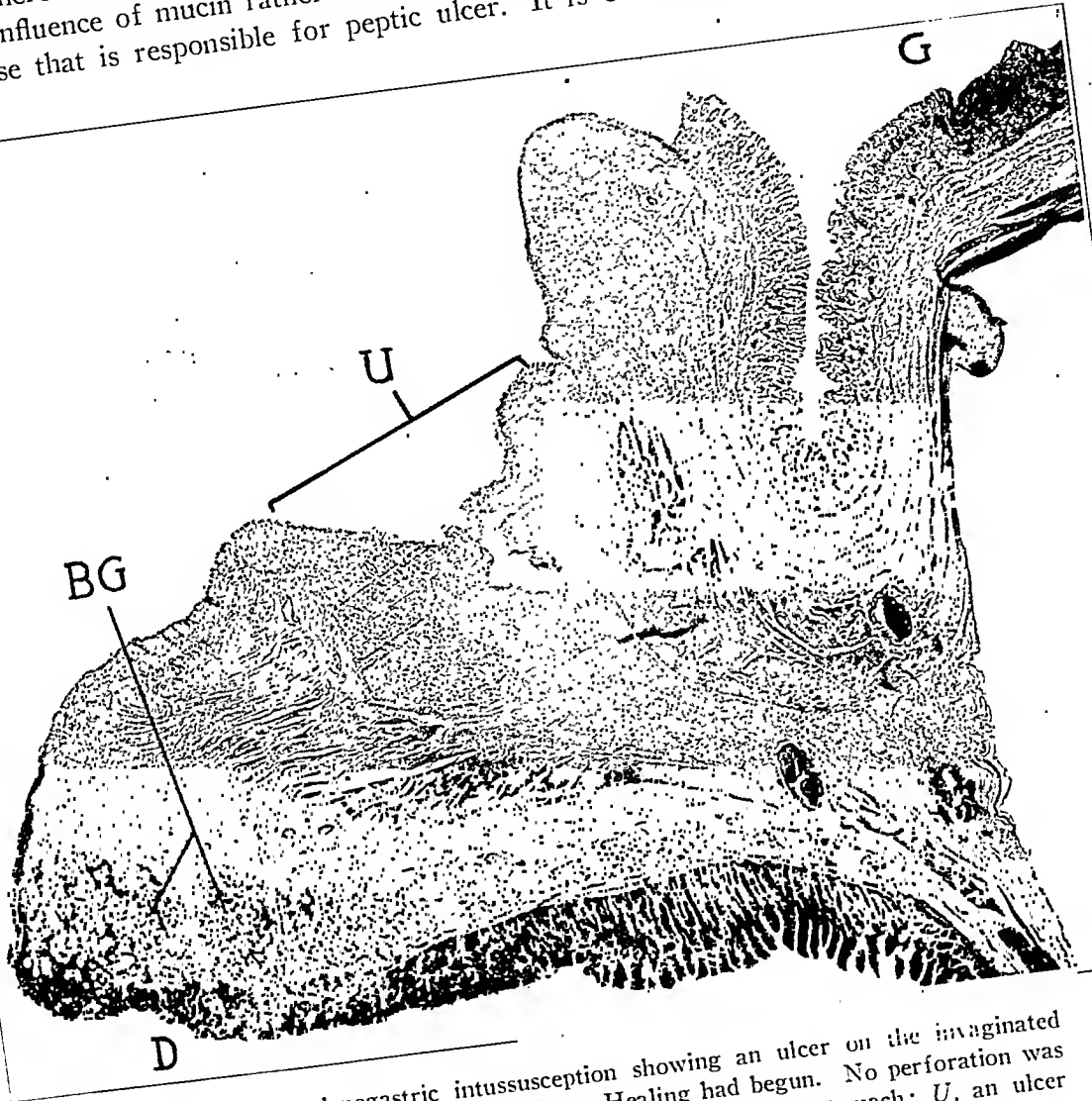


Fig. 8.—Duodenogastric intussusception showing an ulcer on the invaginated portion after toxic doses of cinchophen. Healing had begun. No perforation was found in the stomach or the duodenum. *G* indicates the stomach; *U*, an ulcer on the invaginated portion; *BG*, Brunner's glands, and *D*, the duodenum.

ulcer in man may be the result of an original decrease in acidity which fails to stimulate the glands; or, conversely, an inactivity of the glands that fails to increase the acid and also the mucin content. After ulceration occurs, both are stimulated, but the mucin is inadequate to meet the demands. There may actually exist a premonitory stage of human

peptic ulcer when hydrochloric acid would be beneficial by stimulating the mucin-producing function of Brunner's glands. In dogs that have had toxic doses of cinchophen, we believe that it is the insufficient quantity of mucin, although it is increased, rather than the higher acid content (which was very slight, table 7) that produces ulcers. The mechanism of protection by mucin is beautifully illustrated in the large quantities of ropy saliva that drooled from the mouths of dogs with stomatitis after the administration of cinchophen. Hurst<sup>12</sup> has said:

In hypersthenic persons with a constitutional hyperchlohydria and rapid gastric emptying, the stomach is empty for a much longer portion of the day or night than in the average individual. Accordingly there is much more opportunity for damage to the mucosa by such irritants as alcohol, tobacco and drugs. In addition fractional Ewald meals in individuals of this type show not only hyperchlohydria but also a decrease in mucous secretion. Because of the reduction of the capacity of the stomach to secrete mucous which is characteristic of the hypersthenic constitution, the protection against damage which is afforded by the layer of mucus in the hyposthenic stomach is absent.

Some would argue that if hydrochloric acid is necessary for the production of mucin, why do not ulcers develop in the 10 to 12 per cent of persons who normally have achlohydria? Florey and Harding<sup>8</sup> have shown that even in the complete absence of hydrochloric acid or anything else there is always a normal basic secretion of mucin for the protection of the part. If it is the defense mechanism that is important rather than the increase in hydrochloric acid, an extract of Brunner's glands for parenteral administration may be logically used in the treatment of ulcer provided further experimental work proves this hypothesis to be correct. It is true perhaps that "no acid—no ulcer." But we believe that it is rather the failure of Brunner's glands to protect and neutralize than the high acid content that causes ulcer. When peptic ulcer does occur, it is usually at the site of these glands, and their neutralizing power is still further crippled. Because of this, the acid is relatively increased.

The mere presence of streptococci in the throat does not constitute streptococcic pharyngitis, nor will it so long as resistance is great enough. It is the immunologic panel that must be kept high rather than the uncontrollable bacterial stress that must be kept low, although wholesome environment is not to be shunned. Mucin is the local protector of the tissues against acid, and its presence should be assured in combating peptic ulcer, although here, too, strong irritants affecting the gastric mucous membrane and its acid are not to be encouraged. Our experiment proves the value of reenforcing and using the pyloric end of the stomach in the treatment of ulcer rather than sacrificing it, as is done in gastrectomy or pylorotomy. It would seem that one's duty is to

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12. Hurst, A. F.: The Unity of Gastric Disorders, *Brit. M. J.* 2:89, 1933.

save all the mucous membrane one can, for it is desperately needed. The operation described makes an artificial plica cricularis (valvula coniventes), delimits jetting of acid chyme, secretes mucin and immobilizes the pylorus, permitting the ulcer to heal. For a good many years we have treated perforated duodenal ulcer by pulling the wall of the stomach down over the perforation and suturing it there, as was first suggested by Dr. W. D. Gatch<sup>13</sup> (fig. 1 *A*). We have encountered no recurrences or obstructions at the pylorus after this procedure. We now feel that we may logically apply the same procedure around the entire pyloric circumference, although we have not done so in man.<sup>14</sup> It would immobilize the diseased area, reenforce the pyloric walls and transplant active Brunner glands with their protective mucin. Because of its safety and ease of performance in suitable cases, it would seem to be an aid in the surgical treatment of chronic ulcer. If scarring of the pylorus is marked, or if the ulcer is on the stomach side, excision of the ulcer with part of the pyloric sphincter after the method of Judd, followed by duodenogastric intussusception, may be the operation of most permanent value.

#### SUMMARY

A brief discussion of the prevailing theories of the causation of ulcer is given.

An experimental procedure which we have called retrograde duodenogastric intussusception is described.

As a result of our experiments, together with those of others, we conclude that: (*a*) Brunner's glands have two secretions—a local protective mucin and a systemic acid stimulating hormone. (*b*) Hydrochloric acid stimulates the local production of mucin as well as the gastrin, which in turn assures the necessary hydrochloric acid for this stimulation, thereby perpetuating the cycle.

The adventitious duodenal mucous membrane in our experiment did not show ulcer, even with increased acidity. This, we believe, is due to the defensive mechanism, which is more important than the offensive, just as resistance is more important than the presence of bacteria.

The production of ulcer by the use of toxic doses of cinchophen has been demonstrated. The dogs in which ulcers were so produced had only a slightly higher acid content but a much larger amount of mucin. Since ulcers develop almost uniformly in controls, we believe that the mucin is insufficient to protect the mucous membrane, even though it is greatly increased.

13. Gatch, W. D.: Personal communication to the author.

14. This procedure has been successfully used in man since this article was submitted for publication. A subsequent report will be published after sufficient time has elapsed for proper evaluation of the results of the operation.

Ulcers occur in the stomach or the duodenum of dogs protected by our technic after the administration of toxic doses of cinchophen, but less frequently and apparently without perforation. A study of figure 7 shows the value of extra layers of tissue to guard against perforation.

The suggestion is made that this operation may be of use in the treatment of peptic ulcer in man.

Further experimental work for the purpose of developing an extract of Brunner's glands for parenteral administration is suggested.

# OPERATIVE EXPERIENCE IN CASES OF PINEAL TUMOR

WALTER E. DANDY, M.D.

BALTIMORE

Although an operative approach to the pineal region was proposed by me in 1921,<sup>1</sup> it was not until a decade later (1931) that the first pineal tumor was successfully extirpated.<sup>2</sup> A disastrous toll of seven fatal issues during this long period seemed almost to indicate the futility of further efforts. Yet the same approach was used successfully in a number of cases of tumor of the third ventricle in which, though the lesion was in the same general region, less serious difficulties were offered. In addition to the aforementioned case, successful extirpation has since been performed in two others, thus indicating that the lesion is not entirely hopeless, although it remains one of the most dangerous of all intracranial growths. This seeming success, however, is still further tempered by the fact that in two of these cases the tumor has since recurred, in one after two and one-half years and in the other after three months. Only the last of the three patients remains well, and the period after operation has been only four months. Since the growth in the first case was solid and encapsulated and was extirpated intact, I expected a permanent cure. However, the growth was teratomatous, containing, in addition to the pineal element, ciliated columnar cells of ependymal origin, cartilage and tissue resembling the salivary gland. The tumor in the second case was much larger; it was so soft and cellular and its capsule so thin that it could not be shelled out intact but had to be removed in fragments. The patient died at her home three months later, but permission for necropsy was not obtained. It is, perhaps, more conceivable that cicatrization at the mouth of the aqueduct caused her death than that such rapid recurrence was responsible. The tumor of the third patient was a pure pinealoma and was perfectly encapsulated. It is unbelievable that it can recur, although I felt equally secure in such a prediction for the first case. In that instance, however, the tumor was a teratoma, whereas in this case the growth was a pure pinealoma.

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1. Dandy, W. E.: An Operation for the Removal of Pineal Tumors, *Surg., Gynec. & Obst.* **33**:113, 1921.

2. Dandy, W. E.: *Benign Tumors in the Third Ventricle of the Brain*, Springfield, Ill., Charles C. Thomas, Publisher, 1933, p. 88.



Reports of three cases of pineal tumor in which the patient survived the operation are appended. Particularly of interest are the remarkable transient postoperative sequelae and the absence of recognizable effects arising from the removal of part or all of the main trunks of the internal venous system of the brain.

#### REPORT OF CASES

CASE 1.—*History*.—J. C., a boy aged 10 years, was first admitted to the hospital on Nov. 24, 1931, with the complaint of headache and vomiting.

The family and the past history were not significant.

The present trouble began five weeks prior to admission, with moderately severe bilateral frontal headache and double vision. The patient slept all afternoon and remained in bed two days, during which time he vomited once. He returned to school, but two days later headache, nausea and vomiting returned. During the first week of his illness the mother noticed that he staggered and "did not seem to go where he wished."

For some time he was improved and played with other children. Good days alternated with bad. Then double vision returned, and there were spells of dizziness. A diagnosis of intracranial tumor was made by Dr. George Wright of Pittsburgh.

*Physical and Neurologic Examination*.—The patient was slender and of normal size. The pupils were large and did not react. There was paresis of both the right and the left external rectus muscles. No ptosis was present. A rough test of the visual fields and the perimetric examination, which had been made at Pittsburgh, revealed nothing abnormal. There was papilledema of 4 diopters in each fundus, and fresh hemorrhages covered each disk and the surrounding fundus. The patient was too ill for an audiometer test, but a watch could be heard when placed against either ear. He walked with a wide base and had a suggestion of but not a positive Romberg sign. There was no ataxia. The deep reflexes were exaggerated but equal on the two sides. A slight ankle clonus was detected on the left but was absent when the test was repeated. The Babinski and Kernig signs were absent. Bradycardia (with a pulse rate between 50 and 60) was present throughout the day prior to operation.

*Roentgenographic Examination*.—A roentgenogram of the head showed a large calcified shadow (fig. 1 B) in the region of the pineal body, a probable pathologic finding in a person of the age of the patient and one that should suggest pineal tumor.

*Ventriculography* (Nov. 25, 1931).—The left ventricle, which was uppermost, was tapped, and fluid spurted under tremendous pressure; 75 cc. of fluid was aspirated and an equal amount of air injected. Both lateral ventricles were much enlarged, and enlargement of the third ventricle showed in the anteroposterior but not in the lateral view. It was suspected that the absence of air in the third ventricle (lateral view) was due to the injection of an insufficient amount of air, and because of the history of staggering gait it was decided to explore the cerebellum first and proceed to the pineal region at the same operation if the result of the first exploration was without significance.

The ventricular fluid contained 6 cells, all of which were mononuclears. The Wassermann reaction was negative.

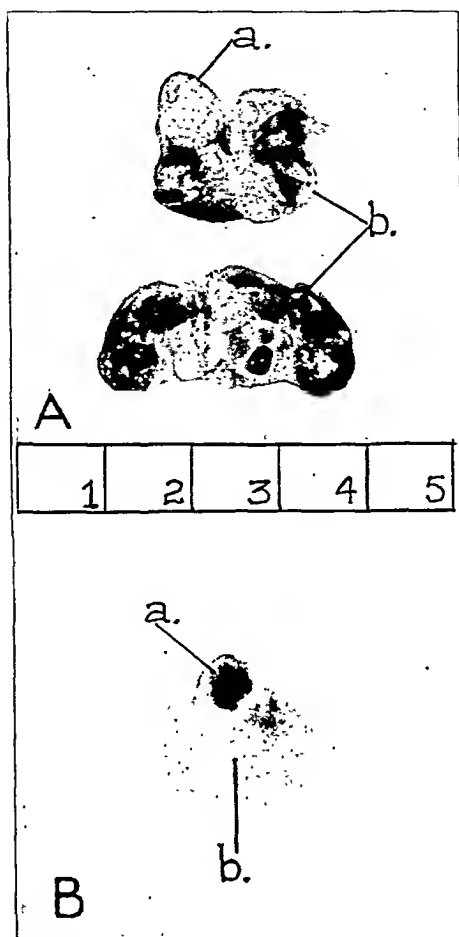


Fig. 1 (case 1).—(A) Photographs of the external surface and cross-section of the tumor, which weighed 3 Gm. The measure shown in the lower portion of the photograph is graduated in centimeters. (B) Roentgenogram of the specimen, showing the dense calcification that was seen on roentgen examination of the head. In these photographs *a* indicates the calcified portion and *b* the cystic portion.



Fig. 2 (case 1).—Photograph of the operative scar, showing the site of operation for a pineal tumor.

*Operation* (Nov. 25, 1931).—Immediately after the ventriculograms had been interpreted, the patient underwent operation under anesthesia induced with tri-bromethanol in amylene hydrate. Exploration of the cerebellum revealed nothing of significance. The fourth ventricle was inspected to the iter. The wound was closed, and a pineal flap was at once made in the right occipital region (figs. 2 and 3). The dura was reflected mesially over the longitudinal sinus. It was not necessary to dispose of any veins crossing from the hemisphere to the longitudinal sinus. After the lateral ventricle was tapped and additional fluid released by gentle compression of the brain, the hemisphere was easily retracted. The corpus callosum was split perhaps three fourths of its horizontal extent. At first, no tumor was visible. The great vein and the two small veins of Galen were in full view. A small circumscribed part of the tumor was then detected just lateral to the small

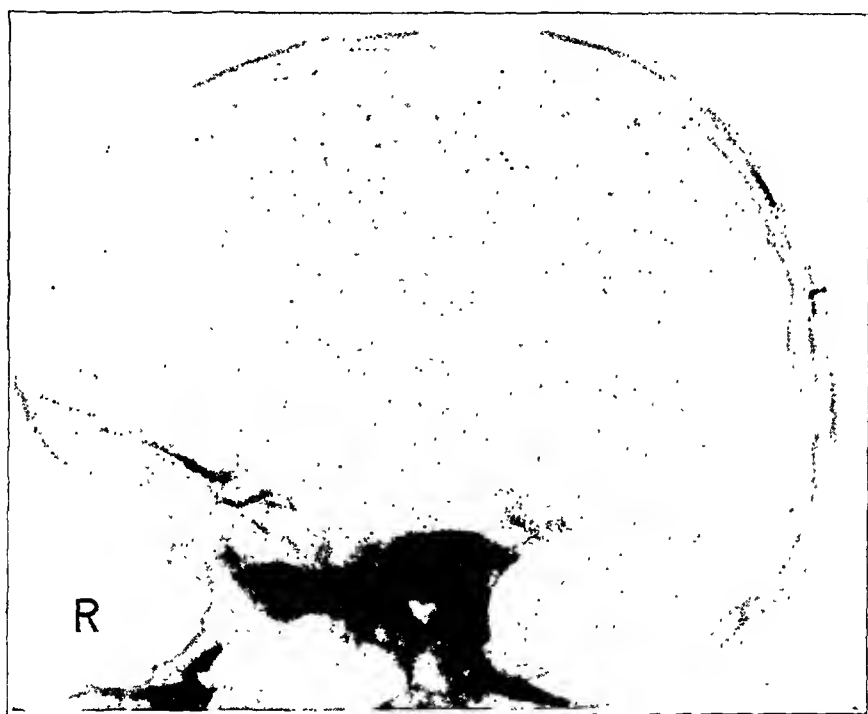


Fig. 3 (case 1).—Roentgenogram of the skull, indicating size and position of bony defect.

vein of Galen on the left and at a point near its junction with the great vein of Galen. With the forceps the left vein of Galen was gently stripped from the surface of the tumor, which was then seen to extend far anteriorly (fig. 4). Fortunately, the attachment of the small vein of Galen to the tumor was slight, so that it could be gently pushed aside. It is worthy of note that the two small veins of Galen were close together in their parallel course (fig. 4); i. e., they were not separated as usually obtains when a tumor lies immediately beneath and is thrust between these vessels.

The tumor appeared to be well encapsulated. It was picked up with the forceps and gently withdrawn between the small veins of Galen, which had been separated by cleaving the thin fibrous tissues between them—the roof of the third ventricle.

As the tumor was gently elevated, a transparent area came into view and was tapped; a few drops of fluid escaped, but the amount was too small to permit impression of its character or color. The capsule of the tumor was again grasped, and with steady traction the tumor was soon delivered from its bed. There remained a slight attachment posteriorly, which for the moment was left undisturbed. As the tumor was delivered up to this point, the third ventricle was opened, and more air and fluid escaped. It could then be seen that the tumor was

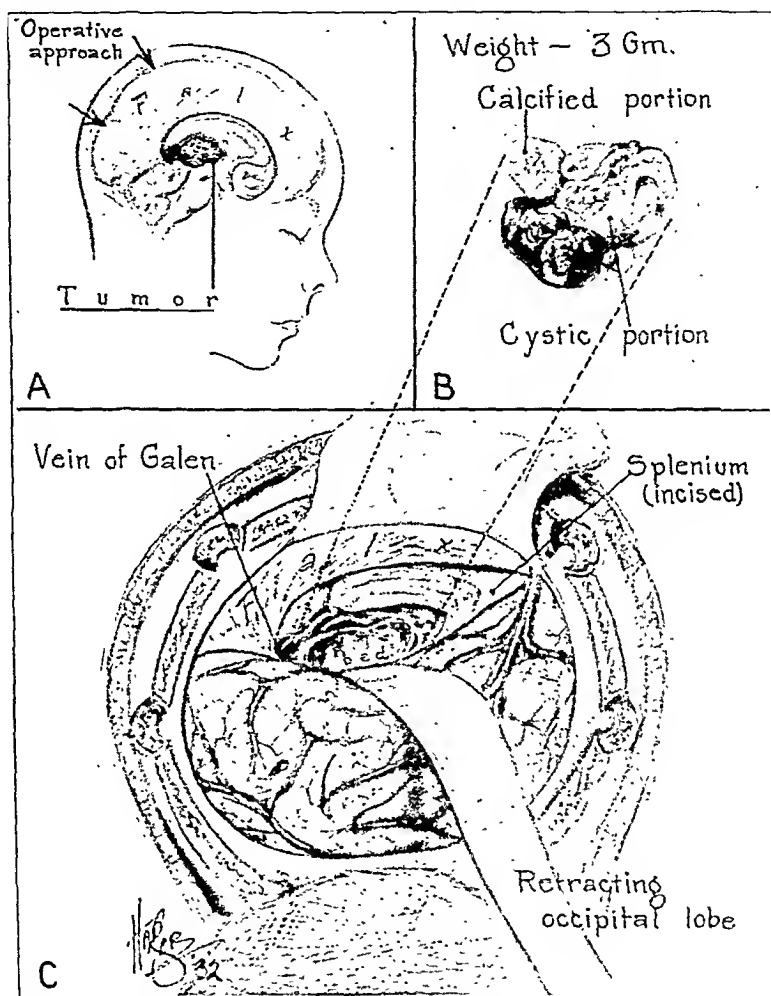


Fig. 4 (case 1).—Drawings showing (A and C) the operative procedure in removal of a pineal tumor and (B) the appearance of the teratoma.

attached posteriorly to the great vein of Galen by a small fibrous band; a small knife divided this bloodlessly. At no time during the removal of the tumor was there any bleeding.

Roentgenograms then showed that the calcified shadow was absent in the pineal region and present in the specimen (fig. 1 B).

*Macroscopic Description of the Tumor.*—The tumor weighed 3 Gm. It was roughly oval and well encapsulated, with a smooth but somewhat irregular surface. From the posterior and upper surfaces of the tumor a small, pear-shaped nodule

(about as large as a pea) projected (fig. 1 *A*), which strongly suggested an enlarged pineal body. At the time the tumor was removed it was looked on as having arisen from the pineal body, largely because of this isolated protuberance. Roentgenograms showed the area of calcification to be in this part of the tumor.

*Microscopic Description.*—In places an ependymal lining could be seen on the outside of the tumor, but usually it was not evident. A heavy external layer of fibrous tissue indicated the capsule. The tumor contained numerous large and small cysts lined with low cubical epithelium, but no basement membrane. Cilia were visible in many places; they were clearly derived from ependymal cells. The basic tissue of the tumor was of loose areolar type (doubtless glia), with few cells; in many places it looked almost like myxomatous tissue. Throughout this fibrous tissue were clusters of large cells with deeply staining nuclei; the cytoplasm was ill defined and sent strands from cell to cell. These were characteristic pineal cells (fig. 5 *A*). Clusters of smaller and more deeply staining nuclei like those

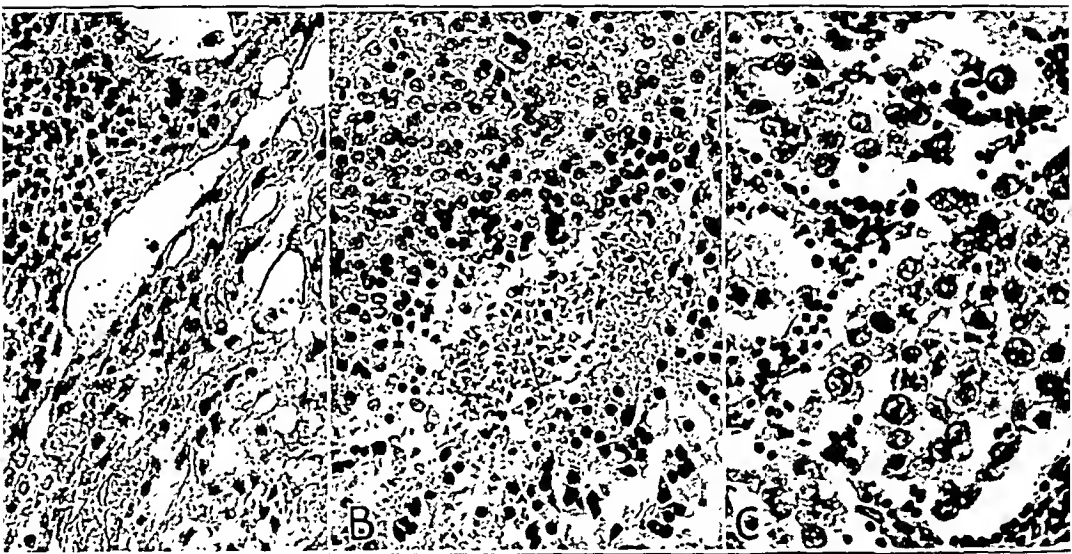


Fig. 5.—Photomicrographs of sections taken from the three pineal tumors described in this paper.

of lymphocytes were scattered throughout (second type of pineal tumor cell), though they were far less numerous than the large cells.

In places were acini of high columnar cells, with basal nuclei and much cytoplasm, which was sometimes vacuolated; such acini suggested the salivary gland. At one point there was a small island of cartilage. Many areas of calcification were present.

*Microscopic Diagnosis.*—The diagnosis was teratoma, with pineal and ependymal cells predominating.

*Further Course of the Illness.*—After the operation the patient was quite ill for ten days; he was listless and voided in bed frequently. Ventricular punctures were necessary for relief of the increased pressure. As the pressure began to diminish, the general condition improved. He then complained that he was unable to see. For the first time, he could see a little on the thirteenth day. At the time

of his discharge from the hospital, on December 14, a rough test revealed that the visual fields were still constricted but that there was no hemianopia (fig. 6). At the time of admission to the hospital vision was known to be greatly reduced, but the patient had been too ill for taking of the visual fields. At the time of his discharge the palsy of the left abducens nerve had entirely cleared, and that of the right was much improved. An audiometer test six days after the operation

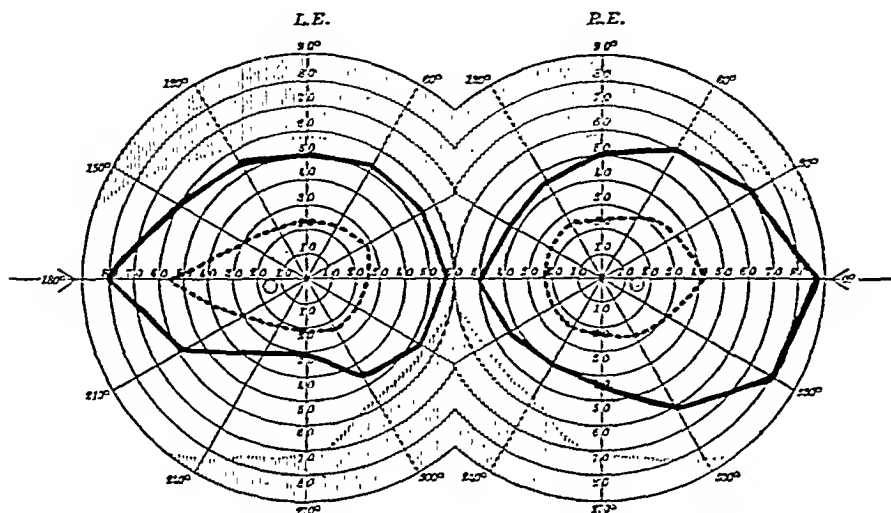


Fig. 6 (case 1).—Visual fields of the patient taken two and one-half years after removal of a pineal tumor. It will be seen that hemianopia did not follow removal of the tumor.



Fig. 7 (case 1).—Photograph of the patient two and one-half years after removal of a pineal tumor, which had recurred during that period.

showed loss on both sides of the upper tones (from 3,000 to 16,000 vibrations)—a finding that made us wonder whether it carried significance as a localizing sign.

*Subsequent Admission to the Hospital (March 15, 1934).*—The patient had grown at a normal rate and appeared normal (fig. 7). He had no extra-ocular palsy, and vision was said to have been normal. He had been playing football and engaged in other sports at school. He stated that he could throw a ball accurately but was unable to catch it.

Two weeks prior to his admission headache and vomiting reappeared; they then disappeared for a week and returned in much the same position as before the first operation. Again, diplopia, stiffness of the neck, unsteadiness on the feet and staggering appeared. The cerebellar region had begun to bulge.

*Neurologic Examination.*—The following findings were of significance: bilateral fixation of the pupils; bilateral paresis of the sixth nerve, probably more marked on the right, and bilateral ptosis. Vision and the visual fields were practically normal. Visual acuity was 20/30+ in the right eye and 20/30— in the left. The audiometer curve, which was of interest during the first stay in the hospital, was unchanged.

*Operation* (March 16, 1934).—A recurrent tumor was removed. Since recurrence of the tumor had been regarded as improbable, the possibility of stricture of the aqueduct was entertained. In order to differentiate between the two condi-

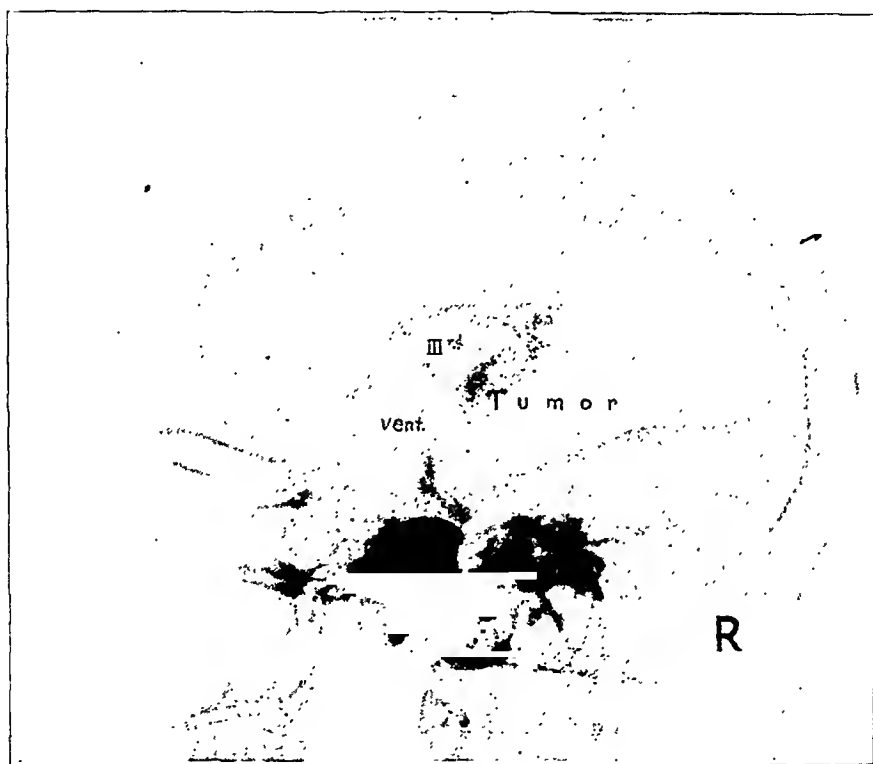


Fig. 8 (case 1).—Ventriculogram showing a filling defect in the posterior part of the third ventricle, due to recurrent teratoma of the pineal body. The original calcified pineal body was absent.

tions, an injection of air was made. One hundred and twenty-five cubic centimeters of air replaced an equal amount of fluid. The fluid was under marked pressure. Ventriculograms showed a large filling defect in the posterior part of the third ventricle (fig. 8), thus demonstrating recurrence of the tumor. The bone, which had healed well, was cut anew. A vein tore at the longitudinal sinus and had to be packed during the operative procedure. Subsequently, when the pack was removed the bleeding was difficult to control, and a fair amount of blood

was lost. The falx was tightly adherent to the mesial surface of the hemisphere. Everywhere, oozing followed separation of the adhesions. A dense mass of adhesions filled the split in the corpus callosum; when these were divided the recurrent tumor came into view. The tumor was smooth and round and, though firmly embedded, could be dislodged without great difficulty or trauma. Again, a small cyst with white gelatinous fluid (indicative of ependymal lining) was evacuated during the delivery of the tumor, which was accomplished by traction on the firm capsule. The tumor was firmly adherent to the great vein of Galen, which tore during the liberation of the mass. It was necessary to thrombose the entire trunk, but this was accomplished without difficulty or much loss of blood. The tumor weighed 6.9 Gm.—more than twice as much as the original tumor.

As the patient had lost a fair amount of blood during the operation and the blood pressure was low, he was given a transfusion of his citrated blood that had been collected during the operation. This was an unfortunate procedure, however, for soon after its administration the blood oozed from all points, owing to the effect of the citrate. It was then impossible to combat the bleeding, and the patient died on the operating table.

The microscopic appearance of the tumor was similar to that of the first specimen, but with much more fibrous tissue. Mitoses were abundant.

*CASE 2.—History.*—H. S., a white woman aged 28, was admitted to the hospital on Aug. 29, 1935, with the complaint of headache and failing vision.

The family and the past history were not significant.

*Present Illness.*—Beginning seven months prior to the patient's admission to the hospital, generalized headache occurred first periodically and then more or less constantly. In the last three months the headache had been much improved, there being only constant dull ache in the frontal region. Three months prior to admission a whirring noise, like that of a motor, developed in the right ear, and this persisted till the time of examination. The patient expressed the belief that there had been some loss of hearing in this ear. Diplopia developed two months before, and for the last two months vision became progressively worse. On two occasions the left upper eyelid drooped for a period of half an hour or more. There were staggering gait and difficulty in control of the finer movements of the hands and arms during the past two months. The patient was generally weak but had no paralysis.

*Physical Examination.*—The patient was well nourished and well developed. The blood pressure was 128 systolic and 80 diastolic.

*Neurologic Examination.*—There were papilledema of 5 diopters in each eye-ground and numerous flame-shaped hemorrhages in the right. The visual fields were normal for form, but no colors were distinguished except with central vision. Visual acuity was 20/40 in the left eye and 20/200 in the right. The pupils were dilated and reacted feebly to light. There was slight, quick lateral nystagmus to either side, but no extra-ocular palsy. The corneal reflexes, though still present, were diminished on both sides. Hearing was somewhat lost in the right ear and was normal in the left. Knee kicks were exaggerated on both sides, more so on the right. The patient staggered somewhat when walking, but the Romberg sign was absent.

*Diagnosis.*—The diagnosis was tumor of the brain of undetermined location.

*Trephine and Injection of Air* (Aug. 31, 1935).—One hundred and twenty-five cubic centimeters of fluid was removed from the ventricular system and an equal



amount of air injected. The fluid was under tremendous pressure. Ventriculograms showed a filling defect in the posterior part of the third ventricle (fig. 9); both lateral ventricles and the anterior part of the third ventricle were greatly dilated.

*Operation* (Aug. 31, 1935).—A pineal approach was made in the right parieto-occipital region. The right hemisphere was retracted from the falx without difficulty. The corpus callosum was exposed and divided. The third ventricle was reached anteriorly; its roof was at once perforated, and a large amount of fluid and air escaped, thus reducing the intracranial pressure. Even then there was inadequate room, so that in exposing the region of the tumor undue pressure had

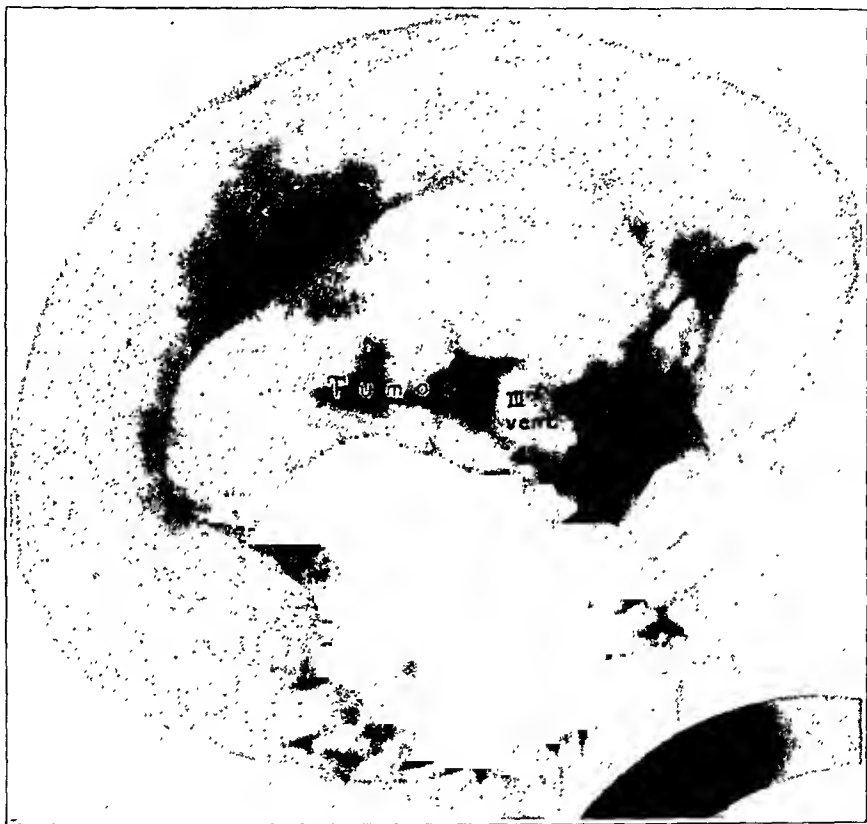


Fig. 9 (case 2).—Ventriculogram showing a filling defect in the third ventricle, similar to that in case 1, due to a pineal tumor.

to be made on the cerebral hemisphere. One could then see the bulging tumor in the region of the great vein of Galen. The small vein of Galen on the right was torn in the attempt to dissect it from the tumor; bleeding from this tear was finally controlled by electrocautery, though with some difficulty. A little later during the dissection the great vein of Galen, which was densely adherent to the tumor, was torn, and it was even more difficult to isolate and thrombose this vessel. Finally, because there was inadequate room, it was necessary to resect quickly the right occipital lobe (fig. 10). Extirpation included part of the parietal lobe, for the transverse plane of the cerebral section was on a level with the great vein of Galen and passed through the anterior part of the posterior horn, exposing the

glomus of the choroid plexus. Little bleeding attended this extirpation. The tumor projected so far posteriorly that it was necessary to resect the tentorium (fig. 10). It could then be seen that the great vein of Galen actually traversed the tumor, and since it had already been thrombosed and divided and additional room was required because the tumor was so large, the incision was made in the

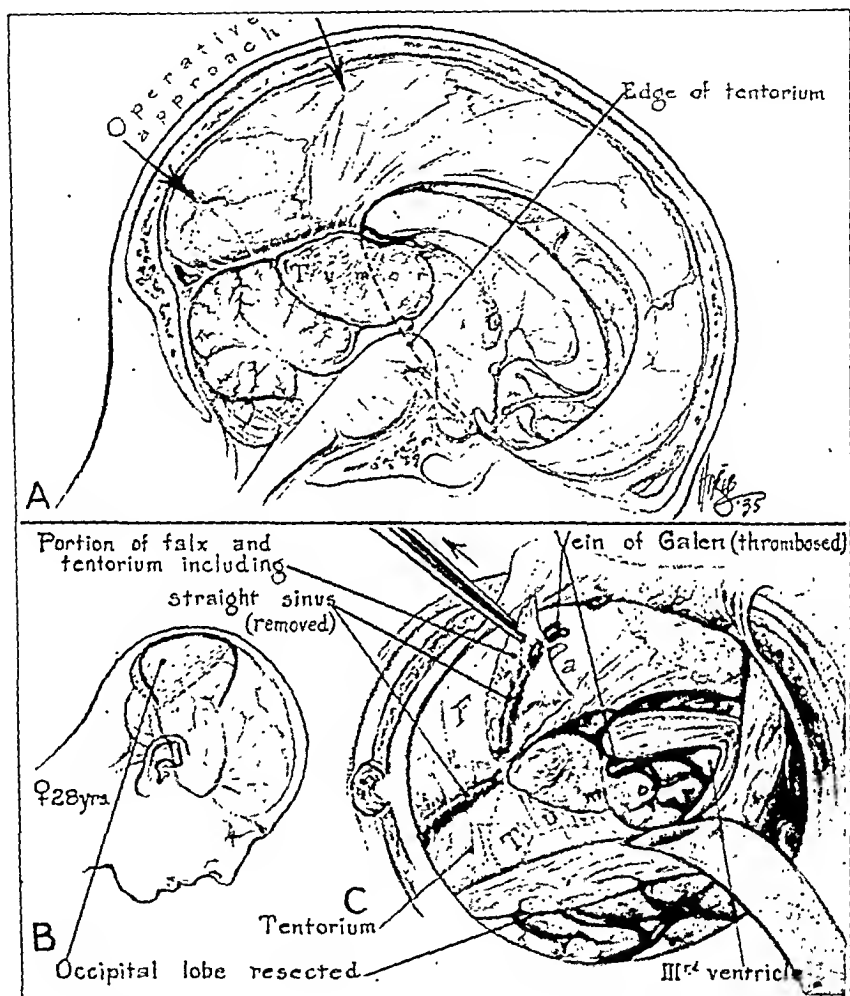


Fig. 10 (case 2).—Drawings illustrating the method of producing more adequate exposure of a large tumor in the pineal region. When the ventricles are relatively small or the tumor is relatively large, the only possibility of carefully extirpating the growth is excision of the posterior part of the hemisphere to provide room.

A shows the relative size and position of the tumor, which extended backward under the tentorium and dislocated the cerebellum; B indicates the amount of the posterior pole of the brain that was removed for the exposure, and C, the method of removing, when necessary, the lower part of the falx, parts of the right and left sides of the tentorium and the straight sinus. The caudal pole of an extensive tumor of this kind cannot be reached without this additional exposure. It will be noted that the straight sinus and the great vein and both small veins of Galen are included in the extirpation.

falx and carried backward to the straight sinus, which was closed by a transfixion suture of silk and divided. The incision was then carried forward into the left side of the tentorium, thus removing a large section of dura overlying the tumor. The tumor was then in full view. The posterior part was dissected away from the cerebellum, into which it protruded but did not infiltrate (fig. 10). The tumor was soft and had a thin capsule which permitted no pull. However, by traction with the spatula it was possible to dissect the tumor from its bed in the quadrigeminal plate and to enucleate it completely. It extended far forward and projected deep into the third ventricle, which it filled completely. During its removal the mass broke into many fragments, but no gross tumor remained. Several small bleeding vessels were thrombosed in the neighborhood of the left vein of Galen.

Since the third ventricle was widely open and had been subjected to sponging, subsequent cicatrization was thought to be a distinct possibility. In removing the tumor, much of it was aspirated through the suction tube. Its soft, cellular nature made it possible to remove much of the interior in this way. The weight of the tumor that was collected, which was but a small fragment of the whole, was 2 Gm. I estimate that the weight of the tumor was about 15 Gm.

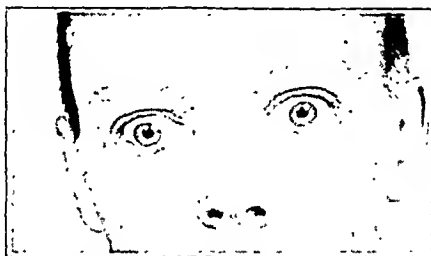


Fig. 11 (case 2).—Photograph of the patient after operation, showing results of severe temporary involvement of all the extra-ocular muscles.

*Postoperative Course.*—The patient was drowsy and listless for a number of days after the operation. Intracranial pressure continued to be high and was relieved by ventricular punctures during the next three weeks. The patient was blind for several days after operation. Vision gradually returned, and at the time of her discharge from the hospital, on September 28, one month after operation, visual acuity in each eye was the same as that at the time of admission. There was, in addition, left homonymous hemianopia. Colors were not recognized. All the extra-ocular movements were restricted but not completely lost (fig. 11); they had steadily improved during the last week. The patient was disoriented for three weeks but became normal in this respect before her discharge from the hospital. Improvement was rapid in every way during the last week.

On Nov. 15, 1935, the following letter was received from her husband: "Until last Friday we had much hope for my wife. On that day Dr. ———, of this city, told me that it was only a matter of time until she died. Doctor, it is tough to see and hear her talking and laughing and know that she has to die. Isn't there something we can do for her?"

A letter was sent in reply to learn in what way she was troubled, and I was advised that she died on Dec. 1, 1935. Permission for autopsy was not obtained.

*Microscopic Diagnosis.*—The diagnosis was pure pinealoma (fig. 5 B).

*CASE 3.—History.*—R. P., a youth aged 15, was admitted to the hospital on Sept. 28, 1935, with the complaint of headache, vomiting and diplopia.

The family and the past history were not significant.

*Present Illness.*—When the patient was 8 or 9 years old (six years prior to his admission) he had periods of severe headache, lasting for several hours and occurring at irregular intervals, but never more frequently than once or twice a week; they were accompanied by vomiting. Four years before he had a fainting spell, but no more information could be elicited; apparently it was not a clonic convulsion. During the past year he was almost free from headache, until two months prior to admission, when the attacks became severe, occurred almost daily and were associated with vomiting; they were generalized but were worse in the occipital region. At about the same time diplopia appeared, and this had remained since. It was noticed that the patient held his head tilted backward and at times complained of pain and stiffness in the neck. He was also said to have walked stiff-legged, but apparently he did not stagger. Photophobia was present during the last two months. At first, he carried on a more or less normal life and was able to play golf. The symptoms gradually became more severe, and a month before his admission he entered another hospital, where he remained for three weeks, at the end of which time he was discharged. Immediately on reaching home, he became much worse and was irritable and drowsy. He was readmitted to the hospital. Lumbar puncture was performed, but no improvement resulted. He then came to Baltimore. On the way he became disoriented, screamed with pain, was extremely listless and talked incoherently.

*Physical Examination.*—The patient was well nourished and of normal development. He was acutely ill.

*Neurologic Examination.*—The neurologic examination was difficult because of the patient's condition. Any attempt at examination made him combative. He saw fingers with either eye. The pupils reacted to light. There was probably slight weakness of the left side of the face of the central type. An audiometer test could not be made. There was marked gross tremor when the hands were used, and the left arm and leg appeared to be somewhat weaker than the right. The biceps and triceps reflexes and the knee and ankle jerks were extremely hyperactive, but more on the left than on the right. Abdominal reflexes were not obtained. There was a definite Babinski sign on the left and an equivocal one on the right; no ankle clonus was present. The eyegrounds could not be examined until the patient was under anesthesia, when high grade papilledema (5 diopters) was found on both sides; there were no hemorrhages.

*Trephine and Injection of Air* (Sept. 28, 1935).—One hundred and fifty cubic centimeters of fluid was removed from the right ventricle, which was lowermost, and 130 cc. of air was injected. The ventricular system was enlarged; this included the anterior half of the third ventricle. There was a filling defect in the posterior half of the third ventricle (fig. 12), indicating the location of the tumor to be in the pineal body. The ventricular fluid was clear and contained no cells or globulin. A small area of calcification showed in the region of the pineal body (figs. 12 and 13).

*Operation* (Sept. 28, 1935).—A pineal tumor was removed. Immediately after the ventriculograms had been read, the patient was placed under anesthesia with tri-bromethanol in amylene hydrate, and a pineal approach was made on the right side. The corpus callosum was split practically its entire length. Fluid oozed

from the subarachnoid spaces surrounding the corpus callosum in large amounts. Finally, the third ventricle was exposed anteriorly and was punctured. An abundance of fluid escaped, providing ample room for the attack on the tumor, which was immediately beneath the corpus callosum (fig. 14). The tumor was white, slightly pink, hard and perfectly encapsulated (fig. 15). The small vein of Galen could be seen skirting the right side of the tumor and, of course, running in a

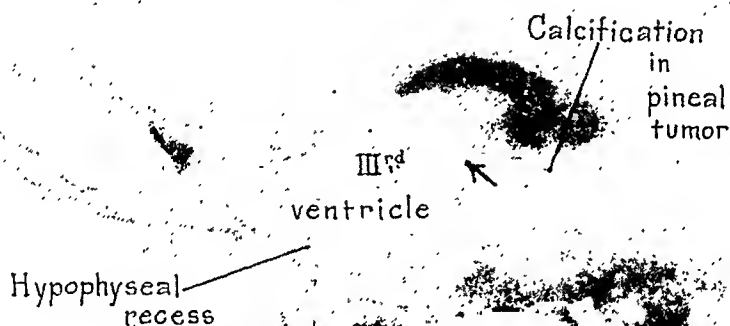


Fig. 12 (case 3).—Lateral ventriculogram showing the degree of hydrocephalus and the filling defect (indicated by the arrow) in the posterior part of the third ventricle. The curved line marks the anterior border of the pineal tumor. There was some calcification in the tumor, and this has been intensified in the sketch.

longitudinal direction; it could be observed as it entered the great vein of Galen and for about 3 cm., where it turned to the region of the foramen of Monro. The small vein of Galen on the left could be seen near the great vein (fig. 14).

It arched around the tumor and was lost to view. An attempt was made to strip the small vein of Galen on the right, but it was bound too tightly to the tumor and finally had to be thrombosed with the cautery and divided at the anterior and posterior pole of the tumor. The capsule of the tumor was then incised, and an attempt was made to extirpate its contents with the curet. The tumor was much too hard, however, and nothing could be accomplished by this attempt. The small area of calcification that showed in the roentgenogram was

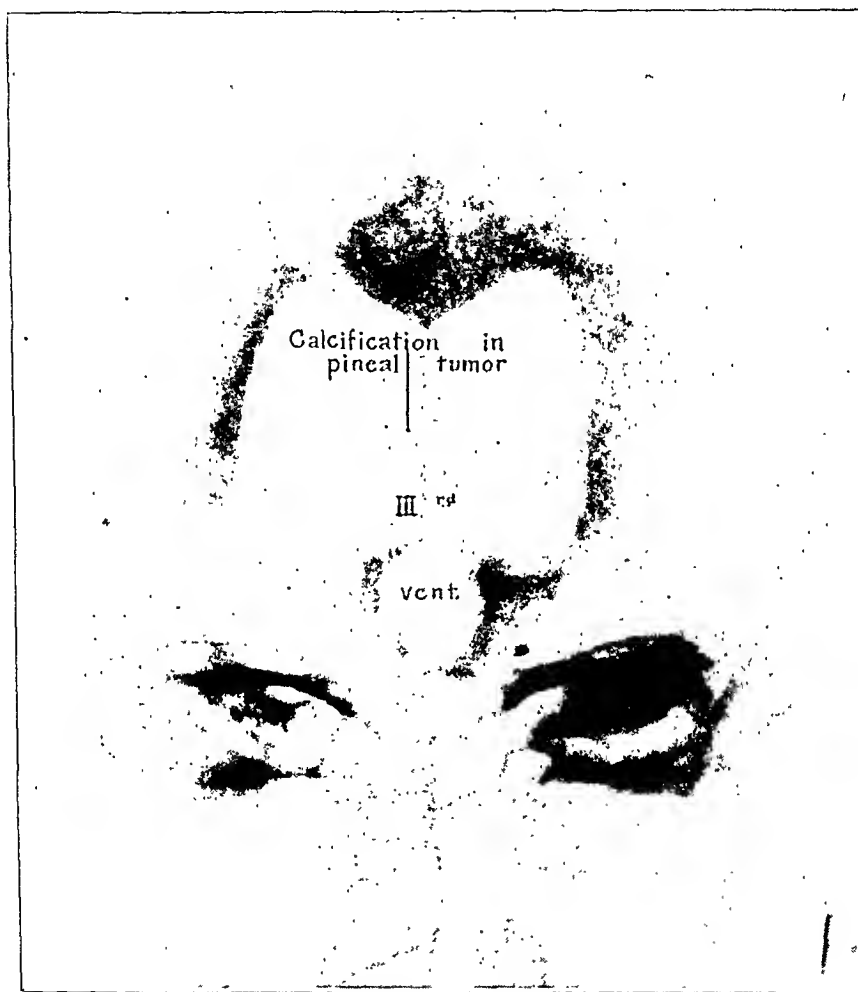


Fig. 13 (case 3).—Anteroposterior ventriculogram showing the proportionately enlarged, mesially placed third ventricle. Only the lateral ventriculogram, with its filling defect, can differentiate a tumor of the pineal body and one of the cerebellum. The position of the area of calcification in the midline of the tumor is evident.

soon encountered, in the posterior part of the tumor (fig. 15). The cutting loop of the cautery was not used, because the application of heat to the brain stem was feared. The firmness of the capsule, however, made it possible to dislocate the tumor by exerting traction on it, and gradually the tumor was elevated and, after much blunt and sharp dissection, was lifted from its bed. It was firmly

embedded in the underlying quadrigeminal plate. Gradually, the left vein of Galen came into view, and it was possible to withdraw the tumor from it without injury. The entire growth lay on the roof of the third ventricle, which was not opened, except anteriorly, where a puncture was deliberately made in order to relieve the excess of cerebrospinal fluid. The part of the tumor attached to the roof of the third ventricle was much less firmly fixed than the portion attached posteriorly. The dense attachment to the quadrigeminal plate required

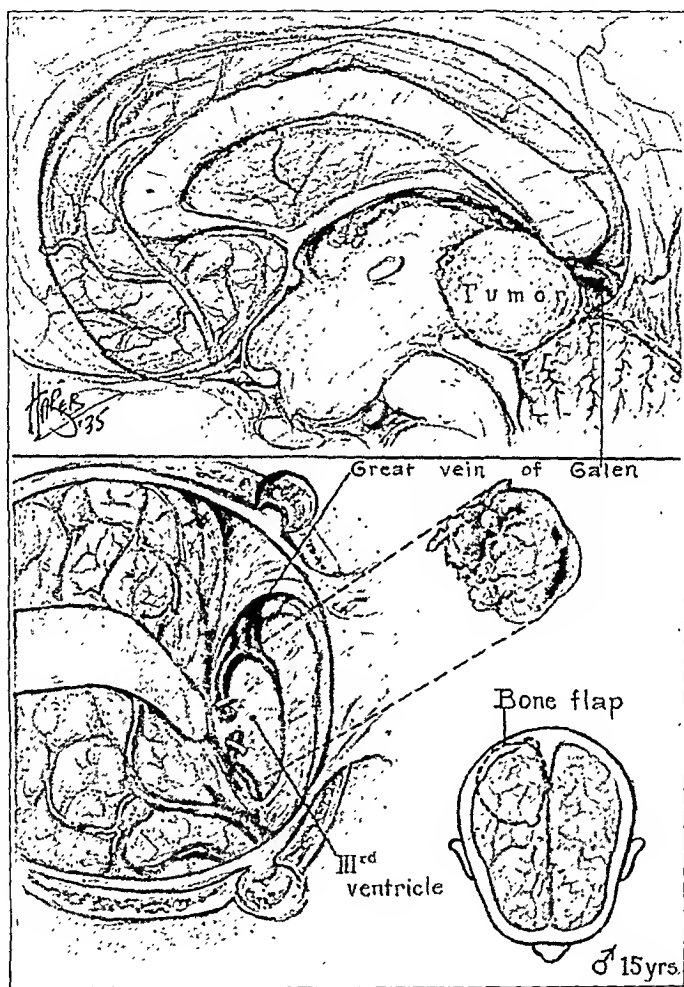


Fig. 14 (case 3).—Operative sketches of a pineal tumor in position in the brain and of the tumor after removal. The small vein of Galen on the right was sacrificed.

numerous applications of fine-pointed scissors and the scalpel before the delivery of the tumor was accomplished. The great vein of Galen was at no time injured. The tumor bulged a little more to the left than to the right. There was almost no bleeding during the removal of the tumor, for its attachments were bloodless. A tiny oozing at the end was traced to a small artery, which was thrombosed with the cautery. The wound was closed without drainage, and the dura and bone were accurately restored.

The tumor weighed 4 Gm. (fig. 15). It was solid everywhere and had slight nodulations on its surface. Histologically, it was a typical pinealoma (fig. 5 C).

*Postoperative Course.*—The general condition of the patient steadily improved. Ventricular punctures were required for seven days. On the second day the patient was thought to be blind, but the pupils reacted slightly to light. There appeared to be weakness in the left arm and leg, although both were used; this seemed a little more evident than before operation. The patient remained totally blind until the seventh day after the operation, when he recognized light and

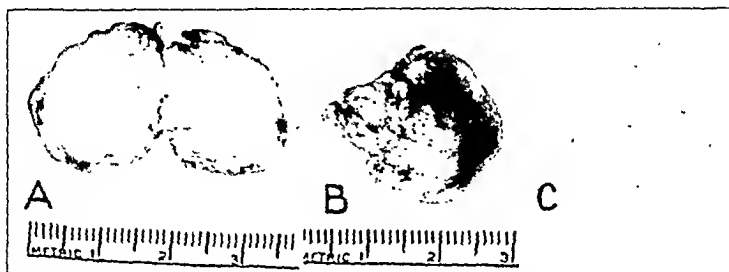


Fig. 15 (case 3).—Photographs of the tumor after removal. *A* shows a cross-section, *B* a surface view and *C* a roentgenogram of the tumor, revealing the area of calcification. The size of the tumor is indicated by the metric tape. The weight was 4 Gm.



Fig. 16 (case 3).—Photograph of the patient shortly before his discharge from the hospital. Conjugate deviation and ptosis were due, no doubt, to edema of the underlying midbrain.

movements of the hand. He sat up on the twelfth day. Vision steadily improved. The mental condition was clear. He was discharged from the hospital on Oct. 12, 1935. Extensive impairment of the extra-ocular muscles and the state of vision were described by Dr. Alan Woods as follows:

"There was conjugate deviation of the eyes to the right (fig. 16); they could be brought back to the midline independently or together, but no lateral motion was possible to the left side. Elevation of the eyeballs and the upper lids was poorly performed; immediately, conjugate deviation of the eyes to the right recurred.



The pupils were dilated and showed only the faintest suggestion of reaction to light. Visual acuity on the right was 20/70, and on the left only movements of the hand were perceived. There was complete homonymous hemianopia [fig. 17]."

I next saw the patient on Dec. 2, 1935, at which time the accompanying photograph was taken (fig. 18 *A*). The Romberg sign was absent. He could walk without staggering. He had no headache and was cheerful and normal mentally. The following report on vision and the extra-ocular muscles was made by Dr. Alan Woods:

"The eyes were normal externally, except for rather widely dilated pupils, which reacted sluggishly to light. Extra-ocular movements showed failure of the left eye to converge, but adduction was normal and lateral movements were normal in every direction, except for the almost abolished upper gaze. Left homonymous hemianopia still persisted.

"Ophthalmoscopic examination showed clear media in both eyes. The disks were flat and of good color, without manifest atrophy, but above and below each disk was residual indication of 'shot-silk' retinitis.

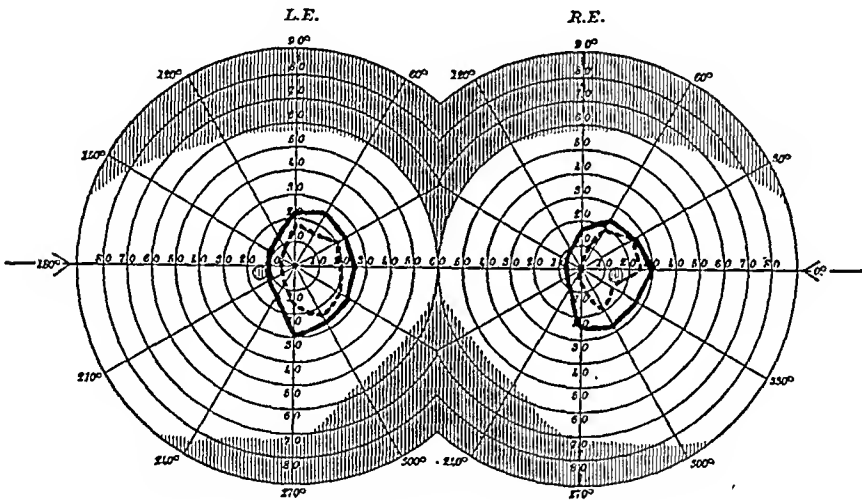


Fig. 17 (case 3).—Visual fields for form and color, taken with a 1 degree test object, showing homonymous hemianopia, which not infrequently follows removal of a tumor in the region of the pineal body and third ventricle. It is doubtless due to traction on the cuneus and is permanent.

"The manifest refraction of each eye was  $-0.37$  sph., with which correction vision was 20/20.

"Tests for muscle balance revealed exophoria of approximately 1 degree for distant vision and of 9 degrees for near vision.

"Diagnosis: At the time of writing the boy presented a rather typical picture of pineal lesion, with involvement of the quadrigeminal plate below, resulting in limitation of upward gaze and disturbances in motility of the pupillary sphincter, due to interruption of fibers to the superior colliculus. The lesion was undoubtedly on the right side, for it probably involved the middle branch of the optic tract to the external geniculate body. All evidence of choking of the disk had disappeared, as had conjugate deviation of the eyes."

## DIAGNOSIS OF PINEAL TUMOR

The diagnosis of a pineal tumor by neurologic signs and symptoms is only occasionally possible. The most significant disturbance is limitation of the upward gaze, the objective evidence of which is ptosis (fig. 19), usually bilateral but at times unilateral; it may be inconstant, particularly in the beginning. Although not a pathognomonic sign, for in some instances a tumor placed anteriorly in the posterior cranial fossa also causes ptosis, it places the burden of proof on tumor other than that of the pineal body. Since in most cases a pineal tumor causes staggering gait, the differential diagnosis of this type and a tumor of the cere-



Fig. 18 (case 3).—Photograph of the patient taken three (A) and four (B) months after operation. Extra-ocular palsy has disappeared.

bellum is always one of great difficulty, and since cerebellar tumor is very common and pineal tumor relatively infrequent, the law of probability has often led to cerebellar exploration, which yielded negative results. The most common clinical story in this series of cases was headache, nausea, vomiting, diplopia and bilateral papilledema—in other words, the signs and symptoms of tumor of the brain, without signs of localization. Fixation and dilation of the pupils were noted in two patients; this condition is probably one of the most important localizing signs; it is also found in cases of tumor of the third ventricle. Three of the patients complained of unilateral tinnitus (one with partial deaf-

ness). The incidence of this symptom is too great to be dismissed as a coincidence.

The ages of the ten patients in this series were 10, 11, 12, 13, 15, 17, 28, 28, 30 and 36 years; in nearly two thirds of the cases, therefore, operation was performed during the period of youth. The earliest symptoms of the existence of a tumor developed in one patient at the age of 9 years; in this case the tumor did not cause dangerous symptoms until six years later. Seven of the patients were males, and three were females. All of the six tumors occurring before the twentieth year were in males. A larger series of cases will be necessary to determine whether these striking figures in relation to age and sex are significant.



Fig. 19.—Photograph showing the degree of bilateral ptosis, which is frequently the most significant neurologic finding in cases of pineal tumor.

Perhaps the most noteworthy localizing sign is an area of calcification in the pineal region of children (figs. 1, 12, 13 and 15). After the age of 20, calcification of the pineal body is an expected and non-significant finding, unless it is of unusual size or intensity. But during youth calcification of the pineal body, while not entirely trustworthy, strongly suggests a tumor and the larger and more dense the shadow the greater the reason for assuming that there is a neoplasm. In four of six children in the present series there was a striking shadow in the pineal region. Curiously, in none of the four adults was the shadow greater than one finds in the normal condition. The area of calcification is therefore significant only in children. The most extreme shadow that I have seen in this region was one in a case of tumor of the choroid

plexus lying in the third ventricle. Tumor in the third ventricle casts a shadow in over two thirds of the cases and in practically the same position, so that the differential diagnosis of tumor of the pineal body and tumor in the third ventricle cannot be made on the basis of the roentgenographic findings. For practical purposes, however, this is not important, for the two require identically the same operative attack.

A precise diagnosis of pineal tumor is probably always possible by ventriculography, but to accomplish this end perfect visualization of the third ventricle is necessary. This is never difficult, because the ventricular system is always greatly enlarged. That one may be assured that the third ventricle will be clearly shown, the fluid in the entire ventricular system must be exhausted and replaced by air; otherwise, the air takes the course of least resistance and passes into the larger cavity, the lateral ventricle. Two ventriculographic changes are probably always in evidence—a filling defect in the posterior part of the third ventricle (figs. 8, 9 and 12) and absence of the suprapineal recess—always a striking space when present. I am not prepared to state that every pineal tumor encroaches on the third ventricle and thus produces a filling defect, but in all the cases that I have observed, it has done so. Every pineal tumor must obliterate the suprapineal recess.

Since the suprapineal recess is not always normally present, one cannot be certain that the absence of this space means the presence of a tumor in this region. But given a suprapineal recess in the ventriculogram, one can be certain that a pineal tumor is not present and that there is either a cerebellar tumor or a stricture of the aqueduct of Sylvius—a lesion by no means uncommon. Therefore, while the absence of the suprapineal recess is significant in a positive way, its presence is pathognomonic in a negative way in excluding the possibility of a pineal tumor. However, since in all the cases of pineal tumor that I have observed a filling defect has been shown in the third ventricle, the obliteration of the pineal recess is of secondary importance.

To obtain perfect filling of the ventricular system, it is necessary only to exhaust the fluid from the lowermost ventricle. It has been stated by enthusiasts for the use of liquids producing opaque shadows (such as thorium dioxide and iodized poppy-seed oil) that the employment of these solutions is especially advisable in the differentiation of tumors in this region because ventriculography (with air) is frequently ineffective. Such a statement is only an admission that the injection of air was not properly made. There is no tumor of the brain causing intracranial pressure, and this includes tumor of the pineal body and tumor of the third ventricle, that cannot be accurately localized by ventriculography. There is never, therefore, in my opinion, justification for the use of opaque material as a means of diagnosis or localization

of any tumor of the brain. It need scarcely be added that spinal injections of air contribute little or nothing to the localization of such a tumor. Always dangerous when intracranial pressure exists, spinal injections of air are particularly so when the brain stem is contiguous to the tumor.

#### OPERATIVE PROCEDURE

The operative attack on pineal tumor is, with minor improvements, essentially the same as that described in the earlier publication. The size of the bone flap is smaller and is situated perhaps a little more posteriorly (figs. 2 and 3). The anterior margin of the cerebral exposure is situated well back of the rolandic vein (fig. 10), and the posterior margin is from about 4 to 5 cm. anterior to the transverse sinus; the usual posterior perforator opening used in ventriculography forms the posterior limit of the cranial defect. The mesial border of the incision in the skin is in the exact midline, and the mesial incision in the bone is made at the outer edge of the longitudinal sinus. Fortunately, this part of the sinus rarely bleeds when uncovered, and with the reduction in the size of the bone flap one can approach the midline directly and without the need of subsequent use of the rongeur. Veins from the cerebral hemisphere to the longitudinal sinus are now much more easily handled by coagulation with the electrocautery (fig. 10). Frequently, there are no such veins, but there may be as many as four or five in the field. If a fairly large vein should be situated well anteriorly and should be placed on a stretch when the hemisphere is separated from the falx, it is usually safer to coagulate it and divide it in the beginning than to run the risk of subsequent tear that would be more difficult to control and, in addition, might well interrupt the extirpation of the tumor at a critical time.

The corpus callosum is split longitudinally from its posterior extremity to a point anteriorly where the third or the lateral ventricle comes into view; this incision is bloodless. Usually this incision takes most, and sometimes all, of this structure to its downward bend (figs. 4 and 12). No symptoms follow its division. This simple experiment at once disposes of the extravagant claims to function of the corpus callosum.

The so-called cerebellar position with the patient recumbent and the face toward the floor is best, because there is need for less retraction of the cerebral hemisphere. The amount of room available for the direct attack on the tumor is in proportion to the size of the lateral ventricles, which, of course, are always greatly enlarged, owing to the obstruction by the tumor at the aqueduct of Sylvius.

Evacuation of fluid from the ventricular system is perhaps the most essential part of the operative procedure. Fortunately, both enlarged

lateral ventricles may be emptied through a single puncture which may be made into the anterior horn of either lateral ventricle (usually the left) or into the anterior part of the third ventricle. It makes little difference at what point the puncture is made. However, a large opening in the roof of the third ventricle should be avoided because of the danger of sponging and injuring the iter. One of the differential points between tumor of the pineal body and tumor of the third ventricle may be that the former (at times only) grows forward over the roof of the third ventricle and the latter, of course, is always under it. Preservation of the roof of the third ventricle greatly facilitates the subsequent flow of fluid through the sylvian aqueduct and therefore shortens the period of convalescence. After the ventricular fluid is released to the utmost, the opening is packed loosely with cotton to preclude the entrance of blood, for a hematoma extending to the remote recesses of the lateral ventricle could not be retrieved. Hydrocephalus, although always present, varies considerably in degree (figs. 8, 9, 12 and 13). The ventricles are always larger in young persons and in patients with a long-standing tumor that has acted as a ball-valve for a time, i. e., in patients with periodic headache and vomiting. The tumors in this series ranged from 3 to 18 Gm. The size of the operative field at the site of the tumor may be greatly reduced by the large tumor; usually, too, a larger tumor develops more rapidly, blocks the aqueduct more promptly and therefore is associated with smaller lateral ventricles at the time of operation. Under such circumstances, there is only one possible way of producing more room—excision of the occipital and part of the parietal lobe, as in case 2 (fig. 10). This we were forced to do in four of the series of cases. Removal of the occipital lobe is the easiest of all lobe resections, because there are usually no large veins (the veins entering the lateral sinus at the mastoid are avoided) and only the posterior cerebral artery requires ligation. Without this expedient there is no possibility of carefully extirpating a tumor, for each forceful retraction of the cerebral hemisphere produces trauma that quickly swells the brain and reduces the field of operation. Needless to say, the infliction of cerebral trauma by operative approach, when the injury is superimposed on trauma at the site of the tumor, leaves little hope that the patient will survive. Sacrifice of the right occipital lobe (because of the possible need of sacrificing an occipital lobe of the brain the operative exposure is always made on the right side) adds more than the necessary room and brings the major part of the tumor directly into view, permitting the operator to use both hands to extirpate the growth.

The need at times of splitting the tentorium longitudinally or the falx vertically and retracting the flaps with sutures of silk has been

stressed in the earlier publication. Resection of part of either structure, or of both, may even be necessary, as in case 2 (fig. 10).

Two factors make the removal of a pineal tumor much more hazardous than that of a tumor of the third ventricle: the tight adherence to the quadrigeminal plate and the much greater intimacy with the veins of Galen. Tumor of the third ventricle is usually only marginally attached at the lateral and posterior borders to the roof of the ventricle and below this merely lies loose in the ventricle, thus making it unnecessary to injure the midbrain or quadrigeminal bodies in the removal. But the entire inferior surface of a pineal tumor is firmly embedded in and tightly adherent to the quadrigeminal plate (fig. 20). Moreover, such a tumor is usually oval, with the long diameter in a longitudinal direction, thus increasing the area of the adherent surface.

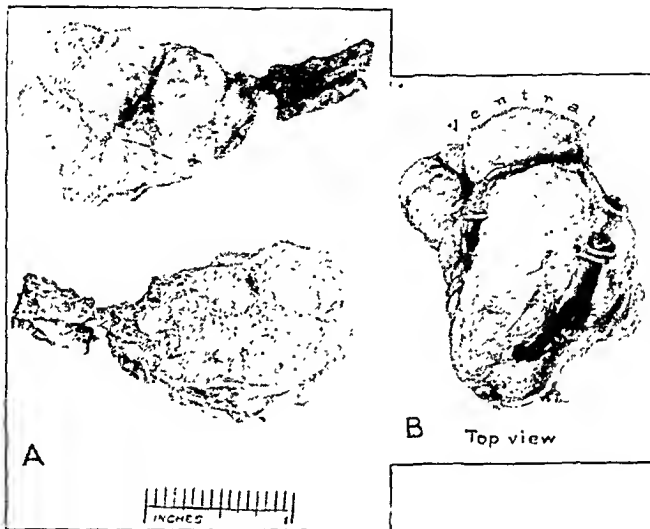


Fig. 20.—Photographs of a pineal tumor. The specimen shown in *A* was totally enucleated, with a section of the tentorium, including the straight sinus and the great vein of Galen, which passed through the growth. The shriveled dura is seen extending from the tumor; the narrow neck is the great vein of Galen. *B* illustrates another specimen in which the great vein of Galen and the two small veins passed directly through and were inseparable from the tumor.

The great vein and the small veins of Galen always lie on a tumor of the third ventricle, but usually the attachment is not difficult to separate and at least one of the veins can be spared. But these veins are usually firmly bound to a pineal tumor and frequently grow into it (fig. 20). In fact, the great vein of Galen had penetrated and was inseparable from the pineal growth in most of the specimens that I exposed at operation (an example of this venous relationship is shown in figure 20).

Liberation of the great vein of Galen and the small vein of Galen on the right (that on the left is not visible at first because it lies beyond the curvation of the tumor) is necessary before enucleation of the tumor can be attempted. This may or may not be possible. When the great vein or its smaller divisions actually traverse the tumor, the operator has no choice other than ligation or thrombosis and division of the great vein of Galen as it leaves the tumor to enter the straight sinus and of the small veins of Galen as they enter the anterior pole of the tumor. But every effort should be made to spare these vessels before resorting to their destruction. Since it was realized that the entire internal venous system of the brain has its outlet through the great vein of Galen, its sacrifice was at first thought to be incompatible with life, although there was no precedent on which such a belief could be established. That none of the first patients who had undergone removal of a pineal tumor survived was not proof that the loss of the veins of Galen was the cause, for other factors may have been and actually were responsible. However, the burden of proof rests strongly on one who denies that this venous system is necessary to life, or at least, to the anatomic and functional preservation of the brain. Instances of thrombi of the straight sinus or the great vein of Galen have, indeed, been reported, but the complete eradication of the major part of these venous trunks is different from the formation of a cicatrix which may allow some restoration of function by collateral channels. Gradually, from the removal of tumors of the third ventricle it was learned that one small vein of Galen could be sacrificed without apparent functional loss (fig. 14). Indeed, it is no simple task to avoid injury to and consequent loss of one small vein of Galen. Although there is less danger of injury to the more distant (left) small vein, its preservation is no mean accomplishment. When intracapsular enucleation of much of the tumor is possible, the loosened capsule can be withdrawn and dissected from the vein, after which the vein remains fairly distant from the field of operation. The near (right) small vein, on the contrary, continues to lie in the line of operative attack and, though protected by moist cotton, is susceptible to operative trauma. The second case in this series of cases of pineal tumor is proof that both the small veins of Galen, the great vein of Galen and at least a third of the straight sinus can be removed without apparent loss of cerebral functions (fig. 10).

After the veins of Galen were disposed of, no large vessels were seen to enter any pineal tumor that has come under my observation. A few tiny arteries and veins enter from the pia covering the quadrigeminal bodies, but one easily disposes of them by packing with moist cotton or by electrocoagulation. However, in some instances the tumor



is quite vascular, and the suppression of blood within the tumor—when intracapsular enucleation is employed—may be tedious and difficult.

The most serious problem in disposing of pineal tumor is freeing the tumor from its bed in the quadrigeminal plate. Too deeply situated to be reached with the fingers, the growth must be liberated with instruments. This is just as well, for enucleation with the finger would cause trauma incompatible with the preservation of life or function. The dangers would be precisely the same as those attending the removal of a tumor of the acoustic nerve. Slow, painstaking extirpation of the tumor from its bed is facilitated greatly if intracapsular enucleation is possible and the capsule is strong enough to support traction with forceps. If one or both of these contributions are possible, traction is made upward from the under-surface of the anterior pole of the tumor with the left hand, and the underlying attachments are liberated by cautious blunt dissection or are divided by the knife and scissors with the right hand. The field must, of course, be constantly dry so that no step is made in the dark. Usually the tumor extends so far posteriorly that additional exposure is required. This is provided by cutting the right side of the tentorium for some distance in a posterior direction and reflecting the mesial cut border over the straight sinus by a traction suture (fig. 10).

Three important sequelae are usual after the successful operative removal of such tumor: intracranial pressure, blindness and extra-ocular palsy (figs. 11 and 16). All these complications are due to edema of the tissues from which the tumor has been liberated, and, if actual injury has not been inflicted, are transient. Although at the time these disturbances are terrifying to the surgeon and patient, they all begin to disappear at about the same time, i.e., a week or ten days after the operation.

The acute intracranial pressure is, of course, due to the edematous closure of the aqueduct of Sylvius. Treatment with ventricular puncture is repeated as often as the condition demands—usually three or four times a day.

Blindness results from edema of the centers of vision in the superior colliculi and the external geniculate bodies. In the early stages of visual return, vision may be present one moment and gone the next, but soon thereafter it is as good as it was before the operation.

It is also of interest that in two of the three instances reported in this paper (cases 2 and 3) a sharply defined homonymous hemianopia to the contralateral side remained permanently (fig. 17). In case 1 the perimetric fields were subsequently normal for both form and color (fig. 6). This sequel of the operation has also been observed in two cases in which tumor of the third ventricle was removed. Although it

is conceivable that injury of the external geniculate body may be responsible, this explanation seems hardly probable, for blindness of this origin resulting from traumatic edema clears a few days after operation. Moreover, there is scarcely less trauma to one external geniculate body than to the other. It appears much more probable that the hemianopia results from retraction of the cuneus during the operation.

Disturbance of the function of the extra-ocular muscles is doubtless due to edema of the nuclei of their nerves and the central pathways in the midbrain. Usually the extra-ocular palsy is unequal on the two sides. As a result, the position of the two eyes is markedly different, and their actions may not be correlated. Conjugate deviation resulted in one case (fig. 16). Restriction of the upward movements of the eyeball—an important diagnostic sign of pineal tumor—was apparently not present in case 3 at the time of admission but has persisted to date, so that the return of extra-ocular muscular function may not be complete. Perhaps this represents the degree of permanent injury resulting from the extirpation of the tumor. It has never been clear how this limitation of movement could be effected alone, i. e., without similar loss in the remaining extra-ocular movements referable to the oculomotor nerve.

#### SUMMARY AND CONCLUSIONS

Three patients with tumor of the pineal body survived extirpation—seemingly total. One patient died three months later (cause undetermined); in the second patient the tumor recurred in two and one-half years, and the third patient is living and apparently well four months later.

In most cases a pineal tumor causes only signs and symptoms of intracranial pressure, due to occlusion of the aqueduct of Sylvius.

Important localizing signs occurring at times are ptosis, usually bilateral, limitation of the upward movements of the eyes and fixation and dilatation of the pupils.

In none of the ten cases were there any disturbances of endocrine character.

Perhaps the most important objective evidence of a pineal tumor in young children—but not in adults—is calcified shadow.

Precise localization in all cases of pineal tumor can be made by ventriculography. The pathognomonic changes are a filling defect in the posterior part of the third ventricle and obliteration of the supra-pineal recess.

Six (60 per cent) of the ten tumors in this series were in children between 10 and 17 years of age.

The weights of the tumors ranged from 3 to 18 Gm.

A pineal tumor is exposed by an occipital approach, separation of the right cerebral hemisphere from the falx and splitting of the corpus callosum.

In cases of large tumor in which the ventricles are smaller, resection of the posterior part of the right cerebral hemisphere is necessary. This method was used in four cases (in three of which the outcome was fatal and in one, successful).

Transient blindness and subtotal paralysis of all the extra-ocular muscles followed operation in each of the three cases in which the intervention was successful. These disturbances disappeared a week or ten days later. They were doubtless due to edema resulting from trauma to the quadrigeminal plate, in which the tumor is always firmly embedded, and to the underlying brain stem.

Left homonymous hemianopia may or may not follow and be permanent. It is probably due to compression of the cuneus during the separation of the hemisphere at operation.

# INTESTINAL OBSTRUCTION PRODUCED BY MESENTERIC BANDS

IN ASSOCIATION WITH FAILURE OF INTESTINAL ROTATION

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During the embryonic development of the human intestine wide change in position takes place before the adult arrangement is obtained. This change in position is designated as rotation. The exact reason for rotation is not known; in fact, embryologic investigations, which consisted of the study of developing embryos 5 mm. or more in length, have indicated that no physiologic reasons are known. Rotation is secondary to the herniation of the midgut into the umbilical cord and apparently is the result of the physical forces inside and outside the hernial sac and of the differences between the physical properties of the small intestine and those of the large intestine at the time they are "sucked back" into the abdomen.

If a patient whose intestine has failed to rotate regularly presents certain digestive difficulties, the nature of these disturbances should indicate the physiologic function which results from the special anatomic arrangement produced by changes in position of the intestine during development. There are no clinical data, however, which indicate that this special anatomic arrangement obtained through rotation is necessary. Failure of intestinal rotation, per se, does not produce digestive derangement. The fact remains that failure of intestinal rotation is a congenital anomaly, and for this reason one may expect it to be accompanied by other congenital anomalies capable of producing digestive disorders.

Congenital anomalies associated with failure of intestinal rotation and capable of producing serious digestive disorders are known to exist. There are two groups of these anomalies: (1) the group in which there is failure of fixation of the small intestine, making possible volvulus of the entire mass of the intestine in a clockwise or counter-clockwise direction about the mesenteric pedicle, and (2) the group in which there are persistent congenital mesenteric bands producing intermittent or abso-

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lute intestinal obstruction. Gardner and Hart<sup>1</sup> reported 2 cases in which the condition was of the first type and collected reports of 105 cases from the literature. In 88 of the 105 cases the condition was the result of volvulus of the entire mesentery, and in 10 cases there was obstruction of the transverse colon which resulted from reverse rotation. In 7 cases the obstruction was of the second type—obstruction of the intestine as a result of mesenteric bands or abnormal intestinal fixation.

It appears to us that volvulus of the entire mass of the small intestine about the mesenteric pedicle which produces obstruction is more likely to arouse interest and be recorded than a mesenteric band which produces intestinal obstruction. The term mesenteric band has been so commonly used to designate any and all sorts of bands in the abdomen that it is perhaps no more descriptive than the term adhesion. A mesenteric band is always congenital and is never the result of peritonitis. It may occur anywhere throughout the extent of the primitive mesentery. In this study we shall present evidence, first, that mesenteric bands frequently accompany failure of rotation of the intestine; second, that these mesenteric bands have definite function during the period of normal development, and, third, that the maintenance of these normal embryonic functions after birth may produce intestinal obstruction. The plan of the study includes consideration of (1) the general aspects of congenital intestinal obstruction, (2) the general anatomic situation of congenital bands as they occur in the abdomen, (3) the development of the primitive mesentery and the situation of its bands and the embryonic development and comparative anatomic study of intestinal rotation and (4) the clinical aspects of 15 cases of failure of intestinal rotation with which mesenteric bands were or were not associated.

#### CONGENITAL INTESTINAL OBSTRUCTION

Congenital intestinal obstruction may be classified like obstruction acquired in later life, that is, as intrinsic and extrinsic. Of the studies on intrinsic congenital obstruction, Tandler's<sup>2</sup> report of 94 cases, exclusive of instances of anal atresia, is one of the most comprehensive. In 33 of these cases the obstruction occurred in the duodenum; in 55 cases, in the jejunum and ileum, and in 6 cases, in the colon. In his studies on early embryonic development in man he observed that the lumens of the duodenum of embryos between 30 and 60 days of age are at least partly closed with proliferating epithelium. After the embryo is

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1. Gardner, C. E., Jr., and Hart, Deryl: Anomalies of Intestinal Rotation as a Cause of Intestinal Obstruction: Report of Two Personal Observations; Review of One Hundred and Three Reported Cases, *Arch. Surg.* **29**:942 (Dec.) 1934.

2. Tandler, Julius: Zur die Entwicklungsgeschichte des menschlichen Duodenum in frühen Embryonalstadien, *Morpho<sup>l.</sup> Jahrb.* **29**:187, 1900.

2 months old the lumen of the duodenum reopens. This observation by Tandler was confirmed by Kreuter<sup>3</sup> and later by Forssner.<sup>4</sup> Kreuter further expressed the opinion that in every case of congenital atresia of the digestive tract in man the condition should be regarded as the result of physiologic and phylogenetic phenomena. Congenital atresia must not be confused with pyloric stenosis and the resulting obstruction in the new-born infant. In this condition the obstruction is caused by hypertrophy of the muscular coats of the intestine and not by atresia. However, not all observers are in accord in regard to the etiology of these forms of congenital intestinal atresia; for example, Schridde<sup>5</sup> examined 50 embryos, the ages of which corresponded to the ages of embryos studied by Tandler, Kreuter and Forssner, and did not entirely agree with the opinion of these investigators that proliferating epithelium closes the duodenum at any time in the course of its development. Seidlin<sup>6</sup> stated, on the basis of the data obtained from his studies, that if there is atresia of the small intestine, the probabilities are one to two that it is of the duodenum. These data are not in accord with those of Tandler, who found that the jejunum and ileum are obstructed more frequently than the duodenum. The foregoing brief review serves to illustrate that there is no agreement as to the etiology or as to the most frequent situation of intrinsic congenital intestinal obstruction.

Cases of both intrinsic and of extrinsic congenital intestinal obstruction are rare. Our interest in this study lies with the latter condition, in which obstruction is produced by ligaments, bands or abnormal fixation of the duodenum and colon and which may originate in one of two ways: The bands may be remnants of embryonic structures which normally disappear, or they may be the result of peritoneal adhesions which have occurred in intra-uterine life. If intestinal bands that produce extrinsic intestinal obstruction are remnants of preexisting fetal bands, which are either of peritoneal or of mesenteric origin, they must have an anatomic situation which corresponds to the site of bands or folds of the peritoneum or mesentery known to have existed at some period of fetal development. On the other hand, if one assumes that these bands are the result of prenatal or postnatal peritonitis, their anatomic situation is not important.

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3. Kreuter, Erwin: Die angeborenen Verschliessungen und Verengerungen des Darmkanals im Lichte der Entwicklungsgeschichte, *Deutsche Ztschr. f. Chir.* **79**:1 (Aug.) 1905.

4. Forssner, Halmar: Die angeborenen Darm- und Oesophagusatresien: Eine entwicklungsgeschichtliche und pathologisch-anatomische Studie, *Anat. Hefte* **34**:1, 1907.

5. Schridde, H., cited by Seidlin.<sup>6</sup>

6. Seidlin, S. M.: Congenital Duodenal Septum with Obstruction, *Bull. Johns Hopkins Hosp.* **37**:328 (Nov.) 1925.

## GENERAL ANATOMIC CONSIDERATION OF MESENTERIC BANDS

Virchow<sup>7</sup> and Morris<sup>8</sup> were the proponents of the theory that fetal peritonitis produces mesenteric bands in the abdomen. In 1853 Virchow mentioned the frequent attachment of the right colic flexure to the under-surface of the liver and gallbladder. He further mentioned anomalous bands from the gallbladder to the duodenum and to the colon. Morris described these bands as "the cobwebs in the attic of the abdomen" and agreed with Virchow as to their general anatomic situation. It is evident that the advocates of the theory that fetal peritonitis is the etiologic agent in the production of these bands admit a definite anatomic situation.

Reference to textbooks of anatomy reveals that there is a definite anatomic situation of these fetal bands, peritoneal thickenings or mesenteric folds. Spalteholz<sup>9</sup> described a band which may be present and which passes from the undersurface of the gallbladder to the lower third of the duodenum or to the jejunum, and from this point to the transverse colon. Piersol<sup>10</sup> stated that the lesser omentum is sometimes described as prolonged across the duodenum to the transverse colon. Cunningham<sup>11</sup> observed a fold which passes from the region of the gallbladder to the transverse colon, across the duodenum. Nagel<sup>12</sup> studied 150 cases at necropsy and observed a cysticoduodenocolic fold in 18 instances. This fold or band was easily demonstrated when present, and the author reasoned that it is a remnant of the caudal extremity of the primitive ventral mesentery. These anatomic observations indicate that there is a fairly definite regional situation of these bands.

If one projects an imaginary line from the gallbladder to the colon before or after intestinal rotation has taken place, this general regional situation is indicated. This imaginary line corresponds to the region and direction of the duodenocolic isthmus. With the preceding preliminary remarks in mind, a review of the pertinent phases of the embryonic development of intestinal rotation is now made.

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7. Virchow, Rudolph: *Historisches, kritisches und positives zur Lehre der Unterleibsaffektionen*, Virchows Arch. f. path. Anat. **5**:281, 1853.

8. Morris, R. T.: *Gall Spider Cases*, Am. Med. **10**:95, 1905.

9. Spalteholz, Werner: *Handatlas der Anatomie des Menschen*, ed. 7, Leipzig, S. Hirzel, 1914, vol. 3, p. 544.

10. Piersol, George Arthur: *Human Anatomy*, ed. 5, Philadelphia, J. B. Lippincott Company, 1916, p. 2104.

11. Cunningham, D. J.: *Text-Book of Anatomy*, ed. 3, New York, William Wood & Company, 1909, p. 1427.

12. Nagel, G. W.: *The Etiology and Importance of the Cystico-Duodenocolic Fold*, Surg., Gynec. & Obst. **37**:365 (Sept.) 1923.

## EMBRYONIC DEVELOPMENT OF INTESTINAL ROTATION

In figure 1 the alimentary canal of a 4.2 mm. human embryo is illustrated. The changes which transform the primitive alimentary canal into the form which exists in the adult are dependent on (1) increase in length, (2) rotation, (3) fixation, (4) differentiation into anatomic and physiologic parts and (5) development of accessory digestive glands. These changes are intimately associated. They are synchronized and occur in regular order. The increase in the length of the intestine is initiated at a very early period. This increase in length is rapid and demands synchronization of movements in order that the parts may be placed so that function is possible. Rotation, which is the movement

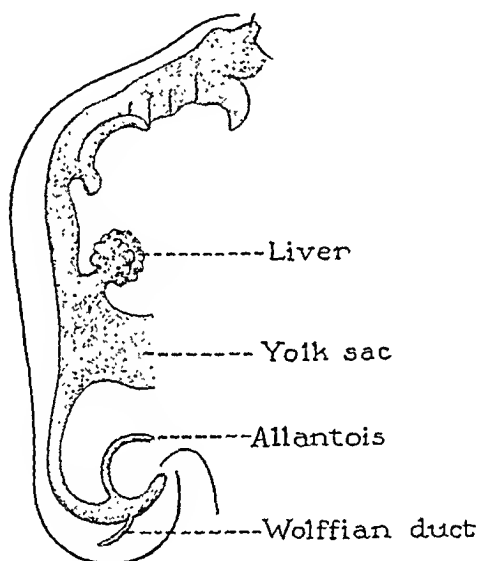


Fig. 1.—Drawing showing the alimentary canal of a 4.2 mm. human embryo (after His).

required to place the parts in functional position, is secondary to increase in length. Fixation is to a large extent secondary to rotation and plays an important rôle in the differentiation of parts and in the anatomic arrangement of the accessory digestive glands situated in the abdomen.

Frazer and Robbins<sup>13</sup> have made comprehensive embryologic studies of the factors concerned in rotation of the intestine in man and have, for the sake of description, divided rotation into three stages.

*First Stage of Rotation.*—In a 7.5 mm. embryo the umbilical loop has been formed and is herniated into the umbilical cord as a result of intra-abdominal pressure and the increasing length of the intestine. By

13. Frazer, J. E., and Robbins, R. H.: On the Factors Concerned in Causing Rotation of the Intestine in Man, *J. Anat. & Physiol.* **50**:75 (Oct.) 1915.



the time the embryo is 10 mm. in length the umbilical loop has turned about 90 degrees to the right, from a sagittal to a horizontal plane. This turning of the umbilical loop to the right is the result of its close approximation to the umbilical vein and the liver and represents the first stage of rotation.

Synchronous with and following the first stage of rotation of the intestine, there is fixation of the duodenum and colon just outside the umbilical hernia. This fixation is accomplished by shortening, narrowing and thickening of the primitive mesentery of the duodenum and colon, which bring these segments of the intestine into close approximation. This area of approximation is known as the duodenocolic isthmus. In figure 2 this region is illustrated schematically. The dotted

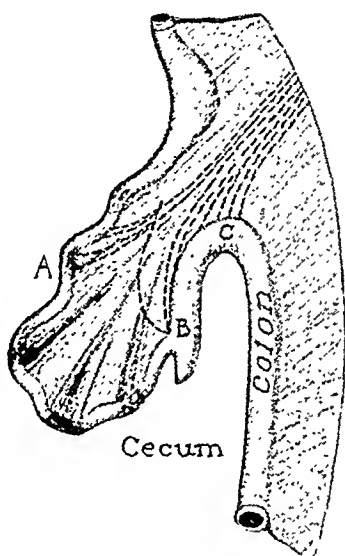


Fig. 2.—Schematic representation of the mesentery of the umbilical loop common to the small intestine and the proximal portion of the large intestine. The dotted lines represent traction bands.

lines in the drawing indicate parts of the mesentery which are more thickened than the rest and which Frazer and Robbins designated as traction bands. These bands exert traction which holds these parts of the intestine in place while the body caudally is increasing rapidly in length.

*Second Stage of Rotation.*—In the second stage of rotation the intestine returns to the abdomen from the umbilical loop. The mechanism of this return is purely physical, and the intestine is literally sucked back into the abdomen.<sup>14</sup> There is a decrease in the rate of growth

14. Mall, F. P.: Development of the Human Intestine and Its Position in the Adult, *Bull. Johns Hopkins Hosp.* 9:197, 1898.

of the liver, an increase in the resistance in the umbilical hernia, which is caused by the ever enlarging intestine, an increase in the pressure of the amniotic fluid outside the hernial sac and a collapse of the lower part of the abdominal wall, all of which combine to produce the sucking back process.

In this stage it is obviously impossible for the intestine to return *en masse*. The best evidence favors the view that the jejunum begins to pass back and is followed by the ileum and, finally, by the colon. Mall observed that the small intestine is back in the abdomen while the colon and the terminal portion of the ileum are still in the sac. The proximal coils of the intestine enter the abdominal cavity to the right of the median portion of the mesocolon, which forms a median septum with the abdominal part of the colon extending above to the central notch of the liver and below to the pelvis. Thus, the coils first fill the lower part of the abdomen below the right lobe of the liver, and by doing so they push the median septum backward and to the left and swing it back so that the remaining coils pass in front of it and come to lie below the stomach, the omental bursa and the left lobe of the liver. When the colon enters the abdomen, it must lie, therefore, with the main vessels above the mass of small intestine.

The wall of the colon is thicker than the wall of the small intestine at this stage of development. The lumen of the colon is also smaller than that of the small intestine, and the colon therefore resists bending better than the small intestine. Such a tube naturally tends to assume the direction of a straight line, and when it enters the abdomen, it tends to come into line with the part already there. Thus, it is disposed to turn to the right. An immediate turn to the right, however, is hampered by its entanglement between the hepatic coils of intestine and the cecum. There are no peristaltic movements at this stage, but the intestines tend to keep their position at the full length of their mesenteries and thus to float the cecum from between their coils. This action of the intestines, combined with the intrinsic tendency to resist bending, places the original umbilical portion of the colon from left to right across the root of the mesentery of the umbilical loop, with the cecum pointing to the right. If, however, the colon returns first to the abdomen, it lies under or dorsal to the duodenum.

Rotation is limited to the portion of the intestine and its mesentery which constitutes the umbilical loop. The duodenum and the abdominal portion of the colon are not involved. The position of the original colic angle in the adult is to the left of the middle of the transverse colon, so that actual rotation of the intestine affects only the portion of the intestine which is situated between the duodenojejunal bend, proximally, and the left of the middle portion of the transverse colon, distally.

It is doubtful whether the changes in the mesentery, the blood supply of the midgut and the folds of the peritoneum can be fully understood from reading the descriptions of these embryonic maneuvers. A clear understanding can be obtained by performing these rotations on one of the lower animals in which the arrangement of the intestine and mesenteries is comparable to that of the human embryo before the second stage of intestinal rotation.

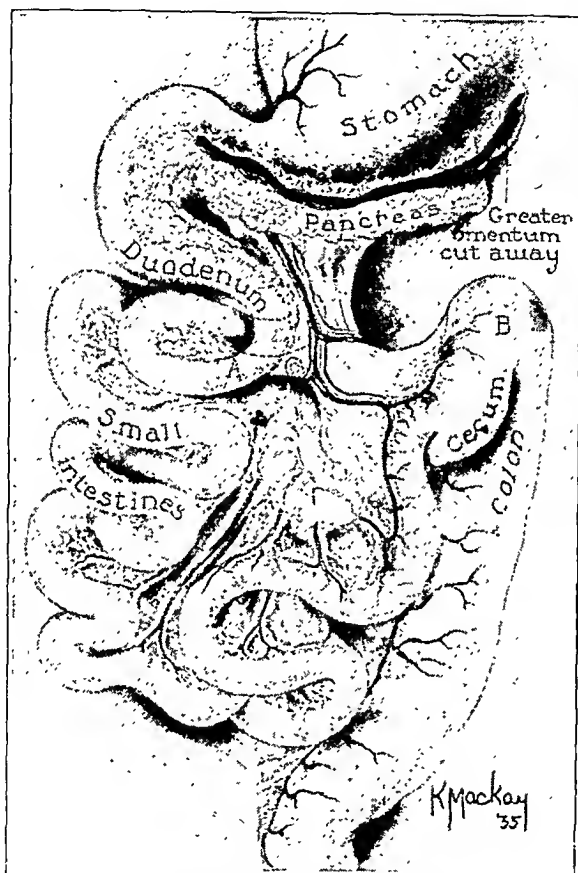


Fig. 3.—Drawing showing the abdominal viscera of the cat (from fresh dissection).

*Comparative Anatomic Study of Intestinal Rotation.*—The common house-cat presents an arrangement of the intestine and mesenteries comparable to that of the human embryo prior to the second stage of rotation. In figure 3 is portrayed the intestinal arrangement of a full-grown male cat. The greater omentum has been cut from the free border of the stomach, and with it the spleen, which occupies the space between the stomach and the colon along the left side of the abdominal wall. The pancreas is spread along the greater curvature of the stomach and

the duodenum, between the leaves of the mesentery. The small intestine is intraperitoneal and has a free mesentery. The ileum enters the colon from right to left, just above the short and pointed cecum. The colon is short but is wholly intraperitoneal and has a free mesentery. It is particularly important to note that the arteries lie to the left of the veins. The space between the duodenum and the colon (*A* and *B*) is the duodenocolic isthmus. It is formed by the shortening, narrowing and thickening of the primitive dorsal mesentery.

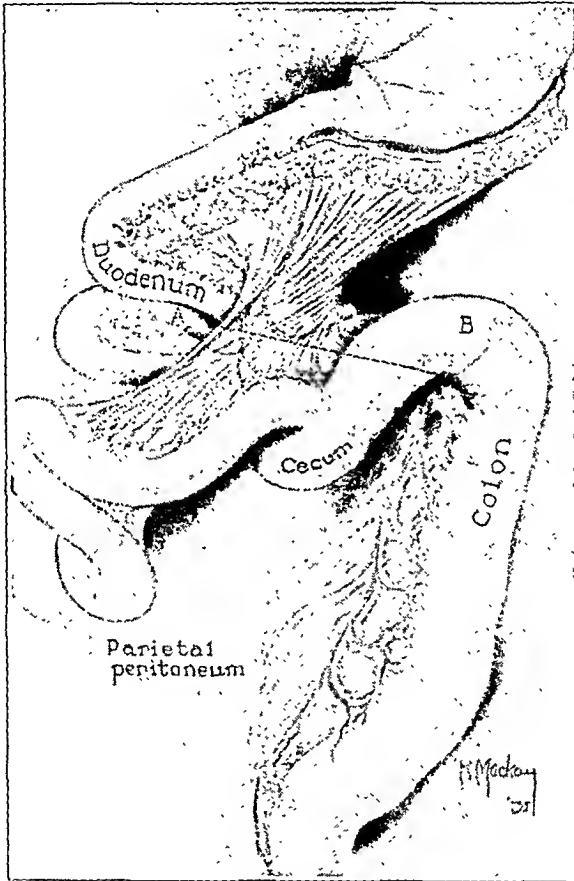


Fig. 4.—Drawing showing the abdominal viscera of the cat (from fresh dissection). The small intestine is pulled to the right to show the duodenocolic isthmus and the extent of herniation of the intestine into the umbilical cord.

In figure 4 is illustrated the mobility of the small intestine on its mesentery. The small intestine has been pulled to the right to illustrate the condition in which the midgut is herniated into the umbilical cord. The dotted line represents the approximate limits of the midgut and the umbilical hernia. The mesentery between the closely approximated segments of the intestine (*A* and *B*) is the duodenocolic isthmus, an important structure to keep in mind. It is about these fixed points of

the mesentery that intestinal rotation takes place normally or fails abnormally. When the intestine is thus pulled to the right, the primitive parietal peritoneum which covers the abdominal wall is seen. This part of the abdominal cavity creates the "empty space," which is important in obtaining the condition necessary for production of the "suction" that forces the intestine to return to the abdominal cavity from the umbilical hernia.



Fig. 5.—Drawing showing the abdominal viscera of the cat (from fresh dissection). The intestine is rotated and held to the left. The colon passes dorsad and anterior to the duodenum.

As shown in figure 5, the second stage of rotation is practically finished. The mass of the small intestine has been lifted to the left, and the cecum has been carried across to the median line. Segment *B* is now directly above segment *A*, instead of to the right. The portion of the mesentery between the segments of the intestine (*A* and *B*) maintains the same relations as the portion shown in figure 4, and the importance of its function as a pivot is evident. The ligament of Treitz is indicated below the region indicated by *A*.

*Third Stage of Rotation.*—In figure 6 the rotation is shown as finished. The small intestine now occupies the left side of the abdomen. The portions indicated by *A* and *B* have changed from the right to the left and from the left to the right, respectively. The ileum now enters the colon from left to right. The descending portion of the duodenum is dorsal to the colon. The superior mesenteric artery, which formerly

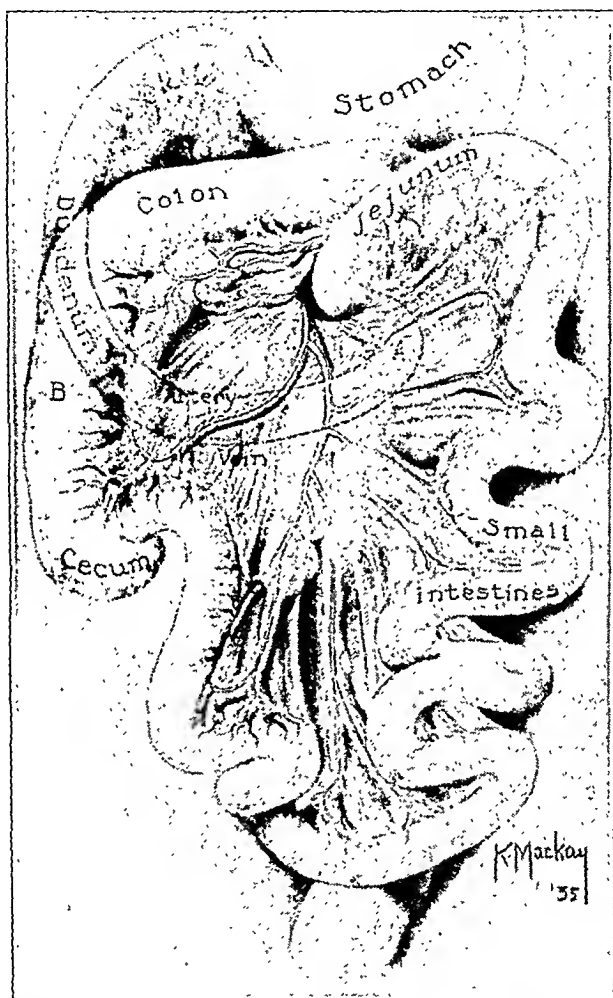


Fig. 6.—Drawing showing the abdominal viscera of the cat (from fresh dissection). The intestine is rotated to correspond to the arrangement in the normal human adult.

occupied the duodenocolic isthmus, now passes anterior to the duodenum. The original branches of the artery on the right are now its branches on the left, and instead of the arteries being on the left side of the veins, as before, they are on the right.

The passing of the colon and cecum from the position they are shown to occupy in figure 5 to that illustrated in figure 6 is termed the

third stage of rotation. In man this increase in the length and extension of the colon so that the cecum occupies the right lower abdominal quadrant may not be finished before the end of the first year of extra-uterine life.

#### REPORT OF CASES

The cases in which there was failure of rotation of the intestine have been divided into three groups: (1) instances in which there were signs and symptoms of intestinal obstruction, without other complicating disease of the digestive tract, (2) instances in which there were signs and symptoms of organic disease of the digestive tract, with or without intestinal obstruction and (3) instances in which definite disease of the digestive tract did or did not exist and failure of intestinal rotation was discovered accidentally on roentgenographic study or in the course of abdominal exploration for other reasons.

*Group 1.*—CASE 1.—A man aged 32 came to the clinic on account of attacks of abdominal pain, which had occurred at irregular intervals since childhood. The pain had been rather diffuse but usually had been more severe on the left side of the abdomen, and it often had followed meals. Once an attack persisted until the patient fasted. Camphorated tincture of opium, he believed, had given more relief than any other means of medication. Between the attacks of pain he had suffered from severe constipation. On roentgenographic examination of the colon a few years before the patient came to the clinic for consultation the entire colon had been reported to occupy the left side of the abdomen.

General examination revealed little of importance. The patient appeared to be in good health. Roentgenographic examination disclosed that the colon occupied the left side of the abdomen. A roentgenogram of the stomach revealed no abnormality. An exploratory laparotomy was performed, and the diagnosis of nonrotation of the colon was confirmed. The part of the colon corresponding to the ascending and transverse segments was pulled upward and to the right in close proximity to the duodenum and was bound behind a mass of adhesions, which were difficult to separate. Postoperative convalescence was satisfactory. Two years after operation the patient had had no further digestive symptoms.

CASE 2.—A woman aged 42 came to the clinic on account of attacks of abdominal pain, which had been accompanied occasionally by vomiting and had been present since childhood. These attacks had appeared at irregular intervals and had lasted from three days to one week. Four years prior to consultation at the clinic she had an attack of "intestinal obstruction," and an exploratory laparotomy was performed. The colon was observed to be dilated and to be situated on the left side of the abdomen.

The patient was in excellent general condition. Roentgenographic examination revealed that the colon occupied the left side of the abdomen. The stomach and duodenum appeared normal roentgenographically. Exploratory laparotomy was performed, and the transverse colon was observed to be attached to the dorsal portion of the parietal peritoneum in the upper part of the abdomen (fig. 7). This produced angulation and obstruction of the colon. The duodenum was intraperitoneal and was sharply angulated, owing to mesenteric bands at the junc-

tion with the jejunum. These mesenteric bands were divided. Postoperative convalescence was uneventful. Six months after operation the patient was in good health. This period was the longest in which she had had no "vomiting spell."

CASE 3.—A woman aged 35 came to the clinic on account of attacks of severe abdominal pain, which had occurred at irregular intervals during the past three years. During the first two years of her illness the attacks had lasted from a few hours to a few days and had been relieved by vomiting. During the past year, however, she had never been free from abdominal pain or discomfort. Alkalis and milk had given only partial relief.

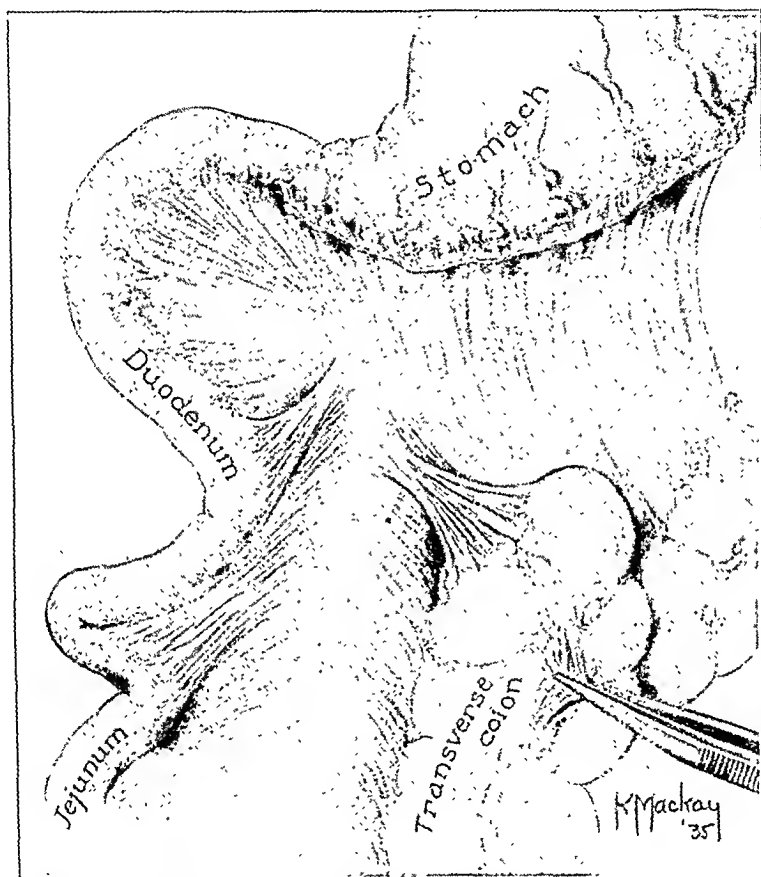


Fig. 7.—Schematic representation of the traction bands in case 2.

She was generally well developed but was poorly nourished. There was diffuse tenderness of the abdomen. Roentgenographic examination revealed that the stomach and duodenum were greatly dilated. An exploratory laparotomy was performed. The enormous stomach and duodenum were situated in close proximity to the middle portion of the transverse colon, which was practically devoid of mesentery. The obstruction had been produced by fixation of the third portion of the duodenum due to mesenteric bands. These bands extended from the duodenum to the region of the gallbladder. The bands were separated. Postoperative convalescence was satisfactory. Five years later the patient was enjoying good health.



CASE 4.—A youth aged 19 came to the clinic on account of abdominal pain and vomiting, which had been present since the age of 2 years. These attacks had occurred fairly regularly every two or three weeks and had lasted for two or three days. The pain during the attacks was moderately severe and was situated just below and to the right of the umbilicus; it reached its greatest intensity immediately after a meal. Once an attack had started, it continued until the patient abstained from food. Three months prior to his consultation at the clinic the appendix had been removed, but the symptoms had not been relieved.

The patient was poorly developed and poorly nourished; otherwise there were no gross physical defects. Roentgenographic examination revealed nonrotation of the colon and a normal condition of the stomach and duodenum. Exploratory laparotomy revealed a firm band, which had caused obstruction at the duodeno-jejunal angle. There was marked dilatation of the mesenteric vessels at this point. Freeing the band did not completely relieve the obstruction, and an entero-anastomosis between the duodenum and the jejunum was performed. Postoperative convalescence was satisfactory, and three years later the patient had gained considerable weight and was free from gastro-intestinal symptoms.

CASE 5.—A man aged 59 came to the clinic on account of severe epigastric pain and vomiting, which had been present for twenty-four hours. In the past he had had similar attacks. About twenty years prior to the present illness he had an attack of severe epigastric pain and vomiting, which incapacitated him for six weeks. After this attack he had been in good health except for an occasional attack of epigastric pain, which soon ceased.

General examination revealed a huge man,  $6\frac{1}{2}$  feet (198 cm.) tall. The blood pressure expressed in millimeters of mercury was 160 systolic and 115 diastolic. The upper part of the abdomen was distended, and there were generalized tenderness and muscular resistance. Exploratory laparotomy revealed considerable free fluid in the abdominal cavity. The first part of the jejunum was distended to a point where it was adherent to the parietal peritoneum posteriorly and almost obstructed. Immediately distal to the obstruction the intestine was collapsed. The colon had failed to rotate. The colon was normal except for its position on the left side of the abdomen. The bands were freed as much as possible, and an entero-anastomosis was performed between the two segments of the jejunum. There were no postoperative complications. One year later the patient was enjoying good health.

In these five cases mesenteric bands obstructed the intestine at one of three points—the lower portion of the duodenum, the jejunum or the transverse colon. The general situation and appearance of these bands are illustrated in figure 8. The situation of the bands in case 2 may be compared with the location of segments *A* and *B* illustrated in figure 3. It is at once apparent that the primitive duodenocolic isthmus was still present and functioning in case 2. A further comparison of the structures shown in figure 8 with the dotted lines in figure 3, which represent schematically the traction bands present in the duodenocolic isthmus, suggests that the dense mesenteric bands in case 2 were persistent traction bands. Thus, on the basis of anatomic studies, we have established our criterion that if a mesenteric or a peritoneal band is to be designated as congenital, it must have an anatomic situation consistent

with the known embryonic structure. The patients in these cases had had symptoms of intermittent intestinal obstruction since they had taken a diet of solid food. Thus, the clinical evidence is definite in incrimination of the traction bands. The fixation of these bands, although a physiologic necessity in embryonic life, becomes a pathologic phenomenon if persisted in after the person begins to take solid food.

*Group 2.*—The second group, consisting of 8 cases, is difficult to describe because surgical exploration was not carried out in all instances.



Fig. 8.—Schematic representation of failure of the second stage of rotation without persistent traction bands.

The patients on whom operation was performed presented definite organic disease other than the mesenteric bands. For these reasons, an opinion will be given in each case as to whether the mesenteric bands were contributing factors in the production of the symptoms.

*CASE 6.*—A man aged 50 came to the clinic for general examination. Since childhood he had had "stomach trouble," which had occurred at irregular intervals and had been associated with "sick headache." There was a family history of

migraine. The "stomach trouble" was described as a heavy, disagreeable feeling in the epigastrium, which occurred about one hour after meals and was relieved by inducing vomiting or drinking hot water. The gastric symptoms became much worse when the patient suffered from constipation. In the past he had had two major heat strokes. The second stroke occurred three years prior to his coming to the clinic, and he had been unconscious for several hours. There had been none of the disabling sequelae characteristic of a major heat stroke.

General examination revealed that the patient was well developed and well nourished and appeared to be in good health. Roentgenographic examination of the stomach and duodenum disclosed duodenal ulcer.

Exploratory laparotomy revealed an inflamed appendix, which was removed. The gallbladder was filled with stones, and it also was removed. The colon and cecum were on the left side of the abdomen, while the small intestine was on the right. Considerable freeing of "adhesions" and mesenteric bands of the jejunum was necessary before a posterior gastro-enterostomy could be performed. Five years later the patient had had no recurrence of the gastro-intestinal symptoms.

This patient had symptoms of intestinal obstruction, which were the result of the mesenteric bands, diseased gallbladder and duodenal ulcer. The duodenal ulcer had not greatly deformed the lumen of the intestine.

CASE 7.—A man aged 31 came to the clinic on account of recurrent attacks of gas pains in the abdomen since childhood. These attacks had occurred at irregular intervals, of from four to six months, and had continued from one to seven days. They consisted of distention, generalized colicky abdominal pain and increasing constipation. In 1926 the patient had a severe attack of abdominal pain, which was accompanied by vomiting. His physician described the vomiting as "fecal." At that time the appendix was removed. In 1929 he had another severe attack; he underwent operation the second time, and a "gangrenous" piece of intestine was resected. For five years after this operation he had been well. In the spring of 1934 he noted return of the abdominal cramps, which occurred at irregular intervals, and he had a great deal of difficulty owing to increasing constipation.

General examination showed nothing of importance, except that the patient was normally developed and of healthy appearance. Roentgenographic examination revealed that the colon had failed to rotate. He was advised to undergo exploratory operation, but he refused.

Evaluation of the symptoms in this case is impossible because the patient refused to permit an exploratory laparotomy. The history of the disturbance, which dated from childhood, revealed that the patient had had intermittent attacks of intestinal obstruction, probably the result of persistent mesenteric bands.

CASE 8.—A woman aged 25 came to the clinic on account of "indigestion and lack of pep," which had been present for four years. Four years prior to her admission to the clinic she had ceased to enjoy her meals; if she ate the stomach became filled easily, and distress followed immediately. There was considerable belching, but this gave no relief. Since the onset of the gastric symptoms, she had suffered from increasing constipation and backache, and there had been slow loss of weight, which amounted to from 10 to 15 pounds (4.5 to 6.8 Kg.). Two

years prior to consultation at the clinic, she had submitted to exploratory laparotomy. The colon was observed to occupy the left side of the abdomen, and the small intestine, the right. The appendix had been removed at this time.

General examination revealed that the patient was of asthenic build; otherwise, she was generally in good physical condition. Roentgenographic examination confirmed the previous observation that the colon had failed to rotate.

The patient was advised to be more careful of her diet and to take better care of herself generally for six months and then to return for further examination and advice. She was never heard from after her dismissal from the clinic.

An evaluation of this patient's symptoms is impossible.

CASE 9.—A woman aged 37 came to the clinic on account of "stomach trouble," which had been present for four years. Prior to this time she considered that she was in good health. The present illness consisted of a dull ache in the epigastrium, which usually occurred at 4 or 5 o'clock in the afternoon and disappeared after the evening meal. There had been remission of the pain in the summer and winter, with exacerbations in the spring and fall. In the past three or four months, the patient had been awakened from sleep by epigastric pain at 1 or 2 a. m.

General examination revealed a tall, thin woman, who appeared healthy. Roentgenographic examination of the stomach and duodenum disclosed a duodenal ulcer and definite pyloric obstruction. Surgical intervention for the relief of the peptic ulcer and pyloric obstruction was advised. Operation revealed a duodenal ulcer, which probably did not produce obstruction. The stomach and duodenum were markedly dilated. Distinct from the duodenal ulcer were many adhesions and mesenteric bands between the transverse mesocolon and the first portion of the jejunum which had to be separated in order to expose the first portion of the jejunum for posterior gastro-enterostomy. The small intestine was entirely on the right side of the abdomen, and the colon, on the left. The obstruction was relieved, and a posterior gastro-enterostomy was performed. The patient recovered from the operation satisfactorily, and eighteen months later she had had no digestive discomfort.

The mesenteric bands were probably contributing factors in the production of the obstruction and symptoms.

CASE 10.—A man aged 40 came to the clinic on account of epigastric pain and distress, which occurred about one hour after meals. For an indefinite period in the past he had had "stomach trouble." Seventeen years prior to his admission to the clinic he had a severe attack of abdominal pain, and an exploratory laparotomy was performed. At that time the colon was observed to be situated on the left side of the abdomen. The appendix was not removed, for it was not inflamed. After the operation the patient was well until about two years prior to his coming to the clinic. At that time he had epigastric pain and distress, which were similar to those which he had suffered prior to the operation seventeen years before.

General examination revealed a large man in good physical condition. Roentgenographic examination revealed that the gallbladder was filled with stones and that the colon occupied the left side of the abdomen. The stomach was normal. At the operation for removal of the gallbladder, an abdominal exploration was made, and the following observations were recorded: There were many adhesions in the lower part of the abdomen. The omentum and two loops of the ileum were adherent to the anterior part of the abdominal wall and also to the duodenum.

These were dissected free, and two small denuded areas of the duodenum were repaired. Postoperative convalescence was prolonged on account of nausea and vomiting. The patient finally made a satisfactory recovery. During the following years he had little digestive discomfort.

No mesenteric bands were present. The symptoms were produced by the peptic ulcer.

CASE 11.—A man aged 35 came to the clinic on account of a dull, burning sensation in the epigastrium, which often extended to the back. The distress occurred when the stomach was empty and was relieved by taking food or alkali. The discomfort had been intermittent for five years and characterized by remissions and relapses. During the remissions the patient had been comfortable. There had been a severe attack of "stomach trouble" two years prior to his admission to the clinic, and at operation, which had been performed elsewhere, an "ulcer was removed." After this operation he had been comfortable for one year.

General examination revealed a small man who appeared healthy. Roentgenographic examination disclosed a duodenal ulcer. Since the patient had undergone one operation and had suffered so much disability as a result of the ulcer, surgical intervention was advised again. He accepted this advice, and at the time of operation a large calloused duodenal ulcer was observed to involve the first inch (2.54 cm.) of the duodenum. There was failure of rotation of the colon. The colon occupied the left side of the abdomen, and the cecum was situated low in the left side of the pelvis. The omentum hung free from the greater curvature of the stomach, and there was complete absence of gastrocolic omentum. Horseshoe kidney was present. An anterior gastro-enterostomy was performed. Recovery after the operation was satisfactory. The patient was not heard from after his dismissal from the clinic.

No mesenteric bands were present in this case. The symptoms were the result of the peptic ulcer.

CASE 12.—A girl aged 11 years was brought to the clinic by her parents, who stated that she had been in good health until about one month before, when she came in from play complaining of pain in the left side of the abdomen. On palpation of the abdomen the mother found "a tumor on the left side the size of a walnut." The child appeared ill, and the temperature at that time was 102 F. Cold applications had given some relief from the pain, but each day since the onset there had been pain in the left side of the abdomen.

General examination revealed that the child was normally developed and apparently healthy. There was a freely movable, hard tumor, about 10 cm. in diameter, just below the left costal margin. Exploratory laparotomy revealed enlargement of the spleen, which was the result of infarction. The affected part of the spleen was removed. The colon occupied the left side of the abdomen, and the small intestine was situated on the right. There were many adhesions around the duodenum and gallbladder, but no evidence of intrinsic disease could be observed in either organ. Postoperative convalescence was good.

The mesenteric bands, if any, and the adhesions produced no symptoms.

Group 3.—The third group consists of cases in which there was failure of the second stage of intestinal rotation. Observation of the

intestinal arrangement was incidental, and there had been no organic digestive disorder. No statistics are available which indicate how frequently failure of intestinal rotation occurs, but no doubt it is not rare. Figure 8 shows the intestinal arrangement in a case of this condition, which was discovered on exploration of the abdomen at the time of a pelvic operation.

Comparison of figure 8 with figure 3 affords a valuable comparative anatomic study. The intestinal arrangement in the two cases is practically identical and functions well; the arrangement in the cat is normal, and that in man, abnormal. It has already been stated that the intestinal arrangement in the cat corresponds with the intestinal arrangement in man before intestinal rotation. This comparison serves to emphasize further the fact that intestinal rotation is not necessary for physiologic function.

CASE 13.—A woman aged 49 came to the clinic on account of umbilical hernia and multiple symptoms which were referable to the menopause. In the past she had had attacks of abdominal pain; however, these were not severe. The attacks consisted of generalized abdominal distress, which occasionally were followed by nausea.

General examination revealed good physical condition. Recently, the cervix had been cauterized, but it was still inflamed. Repair of the umbilical hernia and abdominal exploration and appendectomy at the same time were advised. Abdominal exploration revealed definite inflammation of the appendix. The colon occupied the right side of the abdomen, and the small intestine, the left. The jejunum did not perforate the base of the mesentery. The cecum was mobile. Convalescence was normal.

CASE 14.—A woman aged 33 was first seen at the clinic four years prior to the present visit. At that time there were one or two small fibromas of the body of the uterus, which did not require treatment. She returned, as advised, for reexamination of this condition.

She appeared to be in good health. The uterus had enlarged to three or four times its normal size, and surgical removal was advised. At the time of hysterectomy the appendix was observed to be high on the left side of the abdomen. The colon occupied the left side of the abdomen, and the small intestine, the right. The ileum entered the cecum from right to left. Postoperative convalescence was satisfactory.

CASE 15.—A girl aged 17 came to the clinic on account of "queer spells" and sharp abdominal pain. She had suffered from chronic constipation, with abdominal pain and discomfort, for an indefinite period. Three years prior to her admission to the clinic she had abdominal pain, with nausea and vomiting. She underwent operation for appendicitis but knew nothing of the details of the operation. Jaundice developed after the operation but had cleared rapidly. She had continued to have attacks of abdominal cramps and vomiting. Two years before coming to the clinic she had noted short "queer attacks," during which she "stopped in her tracks"; she had never fallen or lost consciousness. These attacks were made much worse by fright or nervous strain.

She appeared healthy and was in good general physical condition. Roentgenographic examination revealed that the entire colon occupied the left side of the abdomen. The roentgenogram is reproduced in figure 9.

#### FAILURE OF THE THIRD STAGE OF ROTATION

Failure of the third stage of rotation is without symptoms and is usually discovered on roentgenographic examination or at operation. In this stage of rotation the cecum extends to the right lower abdominal quadrant. Variations in the position of the cecum on the right side of the abdomen may be considered to be anomalies of the third stage



Fig. 9.—Roentgenogram in a case in which there was failure of the second stage of intestinal rotation.

of rotation. These anomalies are of practical importance to the physician in acute inflammation of the appendix and to the surgeon in removal of the appendix. If the cecum and appendix are high under the liver, the differential diagnosis of acute appendicitis and acute cholecystitis may be difficult. The surgeon may experience difficulty in locating and removing the appendix through a low abdominal incision.

#### SUMMARY

A study of 15 cases in which there was failure of the second stage of intestinal rotation demonstrates that congenital mesenteric bands

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which are capable of producing intestinal obstruction are commonly associated anomalies. The frequency of this association is not known.

Obstruction of the intestine by congenital bands is produced by maintenance of their known embryonic function of traction and fixation of the segments of the intestine in the region of the primitive mesentery which forms the duodenocolic isthmus.

A consideration of the general aspects of congenital intestinal obstruction and the anatomic situation of congenital mesenteric bands is presented.

A definite visualization of intestinal rotation is obtained through comparative anatomic studies.



# RÔLE OF THE RETICULO-ENDOTHELIAL SYSTEM IN THE DEPOSITION OF COLLOIDAL AND PARTICULATE MATTER IN ARTIC- ULAR CAVITIES

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Many phases of the physiologic activity of the joints are still obscure. Various disturbances in functional activity and pathologic changes which come with disease are understood even less well. The formation<sup>1</sup> and resorption of synovial fluid, with its varying chemical<sup>2</sup> and cytologic constituents, have been carefully studied.<sup>3</sup> The removal of cellular debris or particulate matter<sup>4</sup> introduced into the joint cavity has been followed in experimental animals.<sup>5</sup> Attempts have been made to study the pharmacologic action of certain drugs in relation to articular cavities.<sup>6</sup> This research, while most helpful in advancing knowledge, has not determined how the articular disturbances were initiated or in what manner they could be modified or prevented.

It is commonly believed that noxious substances which disturb articular function are carried to the joints by the blood stream.<sup>7</sup> Studies on lactic acid,<sup>8</sup> uric acid<sup>9</sup> and carbohydrate metabolism suggest this.

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Occasionally, harmful material may be introduced directly into the joint cavity from the outside, or under unusual circumstances flow of lymph may be retrograde.<sup>10</sup> Suppurative arthritis and tuberculosis of joints are regarded in practically all instances as the result of hematogenous infection.<sup>11</sup> Bacteremia with subsequent lodgment of bacteria in capillaries in or about joints is supposedly the origin of such diseases. Recent bacteriologic investigations suggest that an altered response on the part of the tissues may facilitate the development of certain infections.<sup>12</sup> To what extent trauma or other mechanical factors can hinder or encourage bacterial invasion is not fully known. In chronic arthritis one postulates the passage of bacteria or of poisonous substances to the joints, usually from some focus of infection<sup>13</sup> or from the gastro-intestinal tract. In certain cases the articular manifestations may be wholly or in part allergic.<sup>14</sup> It is not clearly understood how the injurious substances enter the blood stream or are in turn removed from it.

Distributed in the loose connective tissues lining the sinusoids of the liver, spleen and lymph nodes, the bone marrow, etc., and also forming a part of the reticulum of the spleen and of the bone marrow, is a host of cellular constituents which can be mobilized as a defense mechanism whenever unusual substances or bacteria are introduced into the body.<sup>15</sup> Certain of these cells are constantly active in health in removing the remnants of dead tissue or metabolic products by phagocytosis, in transporting the material through the blood stream and in storing it, particularly in the liver.<sup>16</sup> From the liver the stored substances are eliminated slowly through the bile into the intestine.<sup>17</sup> The group of cellular elements characterized by the common functions of phagocytosis and the storage of materials of greater than molecular

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11. Wilensky, A. O.: *Osteomyelitis: Its Pathogenesis, Symptomatology and Treatment*, New York, The Macmillan Company, 1934.

12. (a) Coburn, A. F.: *The Factor of Infection in the Rheumatic State*, Baltimore, Williams & Wilkins Company, 1931. (b) Trudel, P. J.: Experimental Bone and Joint Tuberculosis in Rabbits, *Am. Rev. Tuberc.* **28**:331, 1933.

13. Cox, K. E., and Hill, D. F.: Chronic Arthritis: Serologic and Clinical Studies, *Arch. Int. Med.* **54**:27 (July) 1934.

14. Freiberg, J. A.: Allergy as a Factor in the Production of Proliferative Arthritis, *Arch. Surg.* **18**:645 (Feb.) 1929.

15. Maximow, A. A.: Morphology of the Mesenchymal Reactions, *Arch. Path.* **4**:557 (Oct.) 1927.

16. Weatherford, H. L.: The Golgi Apparatus and Vital Staining of the Amphibian and Reptilian Liver, *Ztschr. f. Zellforsch. u. mikr. Anat.* **15**:343, 1932.

17. Jaffé, R. H.: Reticulo-Endothelial System in Immunity, *Physiol. Rev.* **11**:277, 1931.

size, particularly substances of electronegative potential and certain acid dyes used in intra-vitam staining, has been called by Aschoff the reticulo-endothelial system.<sup>18</sup>

The reticulo-endothelial system has widely divergent functions in the body.<sup>19</sup> It participates in all general metabolic actions, especially in the liver. It plays a part in the storage of fats and lipins which is well shown in disease, e. g., xanthomatosis.<sup>20</sup> Probably its most important function is that of active phagocytosis, as shown in inflammatory and reparative processes. Colloidal particles are engulfed and accumulated in granule-like masses in vacuoles within the cell body. Bacteria or other substances may be stored in these cells for appreciable periods, presumably without disturbing the activity of the cell. Violent poisons or virulent bacteria, however, soon destroy the cells which engulf them.<sup>21</sup> It is thought, and experimental proof has been offered by Metschnikoff,<sup>22</sup> Gay<sup>23</sup> and Meersohn,<sup>24</sup> that when the cells of the reticulo-endothelial system are unable to free the body from invading micro-organisms infection takes place. Moreover, local injury of tissues results when toxic substances or bacteria cannot be removed with sufficient rapidity.

Few investigators of the reticulo-endothelial system have made mention of articular tissues. Key<sup>3</sup> has reported the staining of certain synovial cells with trypan blue. Seemen<sup>25</sup> studied the articular absorption of intra-vitam dyes. Raszeja,<sup>26</sup> after making intracardiac injections of a 1 per cent solution of trypan blue, concluded that absorption in articular tissues was dependent on the nature and the degree of dispersion of the injected substance. The studies of Sigurdson,<sup>27</sup> besides those

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18. Aschoff, L.: *Lectures in Pathology*, New York, Paul B. Hoeber, Inc., 1924.

19. Sacks, B.: *The Reticulo-Endothelial System*, *Physiol. Rev.* **6**:504, 1926.

20. Rowland, R. S.: *Xanthomatosis and the Reticulo-Endothelial System*, *Arch. Int. Med.* **42**:611 (Nov.) 1928.

21. Domogk, G.: *Untersuchungen über die Bedeutung des retikulo-endothelien Systems für die Vernichtung von Infektionserregern und für die Entstehung des Amyloids*, *Virchows Arch. f. path. Anat.* **253**:1594, 1924.

22. Metschnikoff, E.: *Sur la lutte des cellules de l'organisme contre l'invasion des microbes*, *Ann. Inst. Pasteur* **1**:321, 1887.

23. Gay, F. P.: *Local or Tissue Immunity*, *Arch. Path.* **1**:590 (April) 1926.

24. Meersohn, J.: *Die Streptokokkensepsis und das retikulo-endotheliale System*, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **54**:313, 1928.

25. Seemen, V.: *Versuche mit Vitalfärbung an Gelenken*, *Zentralbl. f. Chir.* **53**:2603, 1926.

26. Raszeja, F.: *Recherches histologiques sur la synoviale*, *Bull. d'histol. appliq. à la physiol.* **11**:97, 1934.

27. Sigurdson, L. A.: *The Structure and Function of Articular Synovial Membranes*, *J. Bone & Joint Surg.* **12**:603, 1930.

of Rynearson<sup>28</sup> and Key,<sup>4</sup> have shown that materials of larger than molecular size injected into joints are taken up by free histiocytic cells and by phagocytic cells on the surface of the synovial membrane.

The activities of the reticulo-endothelial system in and about the joints constitute the problem of the present study. The young albino rat was chosen for experiment because it is a very satisfactory animal for use in investigations of this system. Observations were made on the nature and extent of the deposition of colloidal and particulate matter in and about the joints following subcutaneous injections. Further studies were made to determine how this deposition could be modified by trauma, irritation, inactivity or attempted local blocking of the reticulo-endothelial system. Finally, the deposition of material in articular cavities after absorption from the gastro-intestinal tract was observed. It was hoped that some relationship might be established between the results of these studies and the problems of articular infection and of disturbances in joints associated with systemic disease, such as chronic arthritis.

#### DESCRIPTION OF EXPERIMENTS

EXPERIMENT 1.—Four rats were given subcutaneous injections of 2 cc. of a 1 per cent aqueous solution of trypan blue every other day. The injections were made into the abdominal wall, and the area was massaged gently to insure more complete absorption. The four animals were given ten, eleven, thirteen and fourteen injections, respectively. Usually after several injections they turned a dusky blue. With long continuation of the injections they began to lose weight; they ate less well and were less active; the hair became rough and was gradually lost. At this stage the animals became moribund.

At necropsy there was noted extensive staining of the entire skin and subcutaneous tissue, as well as of the liver, spleen, kidney and bone marrow. The joints showed a moderate amount of staining. Both femorotibial and humeroulnar joints were removed for microscopic examination. The tissues were fixed in solution of formaldehyde diluted with water (1:9) and decalcified carefully in a 5 per cent aqueous solution of tri-chloroacetic acid in order to avoid undue solution of the stored dye. Sections were stained with paracarmine or with hematoxylin and eosin.

The amount of dye observed in the articular tissues was roughly proportional to the number of injections of trypan blue. After single injections or a few injections during the preliminary studies practically no dye was present in the articular tissues. Most of the trypan blue was deposited in the superficial part of the synovial membrane; less was observed in the deeper parts. Histiocytes stored the greater part of the dye in granule-like clumps in cytoplasmic vacuoles. In fibrocytes the dye appeared in the form of fine granules or short rods. The fat pad of the knee was almost devoid of dye-laden histiocytes. A moderate amount of trypan blue was scattered throughout the reticulum of the bone marrow, almost wholly in histiocytes. None was seen in either bone or cartilage cells. A slight

28. Rynearson, E. H.: The Macrophage in Absorption from the Synovial Cavity, *J. Bone & Joint Surg.* **13**:127, 1931.

increase in the fibrous tissue was observed, but there was very little evidence of an inflammatory response within the joint itself. Individual variations in the amount of trypan blue were found in the joints, as might be expected. The animal that had received fourteen injections showed the largest amount of dye deposited in the synovial membrane.

This experiment, besides its preliminary results, shows that material of larger than molecular size can be carried from the skin and subcutaneous tissues and stored in the joints. The material is transported, probably dissolved or in suspension, by the tissue fluids to the blood or lymphatic stream.<sup>29</sup> Lewis<sup>30</sup> has shown that dissolved trypan blue is precipitated in the blood stream and that the agglutinated particles are then taken up by the cells of the reticulo-endothelial system. All avail-

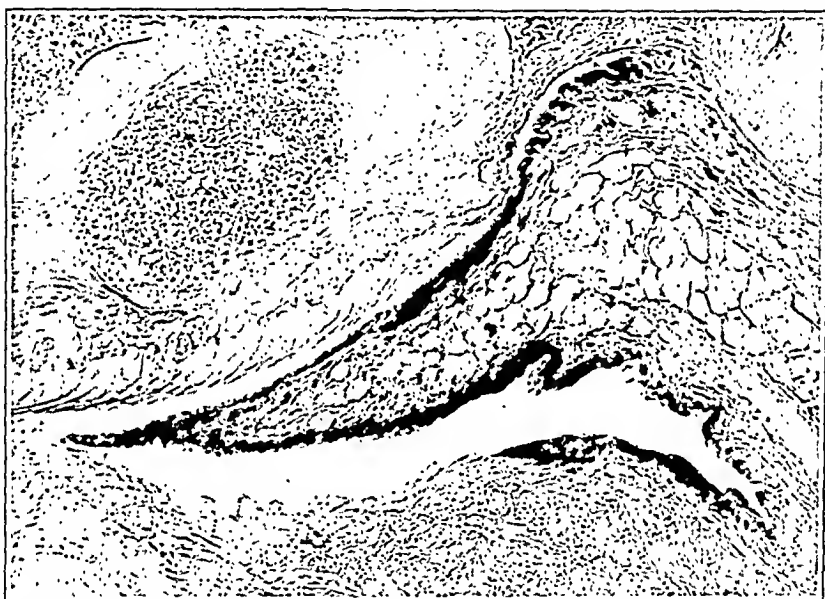


Fig. 1.—Photomicrograph of the knee joint of an albino rat after fourteen subcutaneous injections of trypan blue. Deposition of particles of dye in histiocytes is marked in the superficial layers of the synovial membrane.

able evidence suggests that bacteria,<sup>31</sup> metabolic products not in solution and tissue debris are handled in a similar manner.

EXPERIMENT 2.—A study was made on the absorption of a mixture of dyes, the particles of which varied from the ultramicroscopic (trypan blue) through

29. Field, M. E., and Drinker, C. K.: Conditions Governing Removal of Protein Deposited in Subcutaneous Tissues of Dog, *Am. J. Physiol.* **98**:66, 1931.

30. Lewis, M. R.: Origin of the Phagocytic Cells of the Lung of the Frog, *Bull. Johns Hopkins Hosp.* **36**:361, 1925.

31. Siegmund, H.: Das Retikulo-Endothel und seine Leistungen im Lichte der Vitalfärbung, *Jahresk. f. ärztl. Fortbild.* **18**:5, 1927.

particles at the limits of microscopic resolution (sodium carminate) to particles readily seen by the lower magnifications of the microscope (india ink). Two cubic centimeters of a mixture of equal parts of a 1 per cent solution of trypan blue, a 1 per cent solution of sodium carminate and a suspension of filtered india ink diluted with equal parts of distilled water was injected subcutaneously into two rats biweekly, seven and eleven times, respectively. The mixture was absorbed much more slowly than trypan blue alone. After a few injections there was

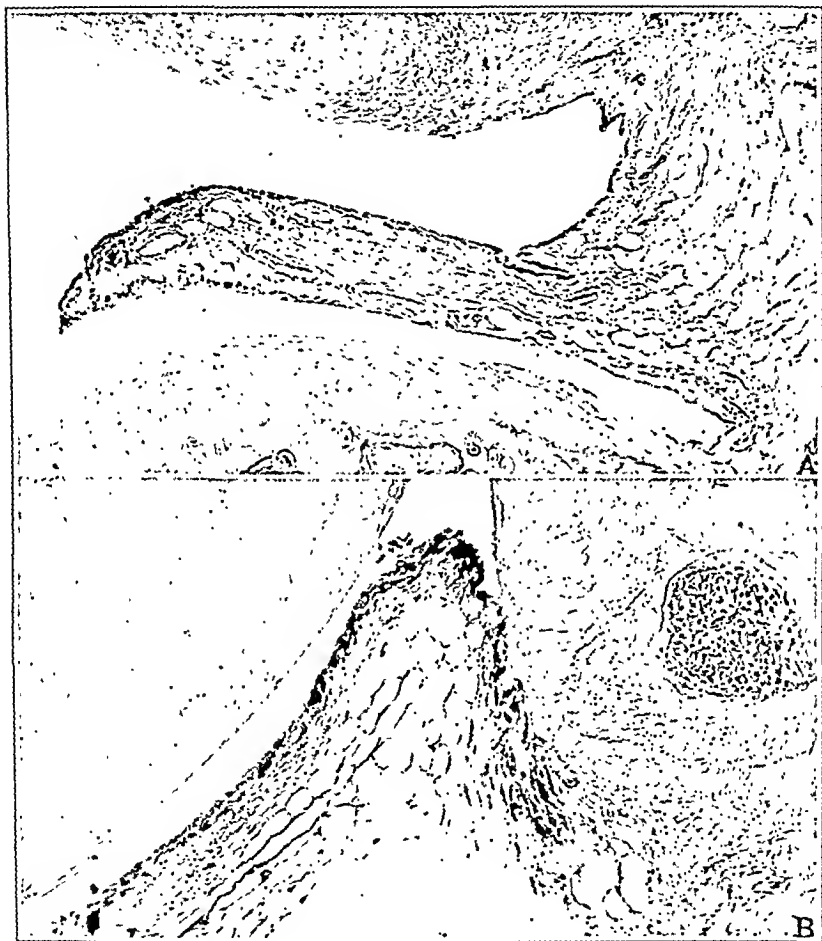


Fig. 2.—*A*, photomicrograph of a villus from a normal knee joint of a rat. *B*, knee joint of a rat which had been given twenty subcutaneous injections of trypan blue simultaneously with twenty intra-articular injections of a 20 per cent solution of potassium iodide. The dye-laden histiocytes are present in parallel layers on the synovial surface, and there is an increase of connective tissue.

necrosis of the skin at the site of injection. Because of the marked irritation caused by the mixture, no further injections were made.

Microscopic studies of the joints of these rats showed much less deposition of trypan blue than had appeared in the joints of the preceding group. The dye was found chiefly in histiocytes. There was only a small amount of sodium carminate

deposited in the cells. No india ink was seen in the articular tissues. As no extended study could be made because of the marked local toxicity, definite conclusions cannot be drawn; but the histologic observations suggest a lessened absorption and deposition in articular tissues of granules in proportion to the size of the individual precipitated particles.<sup>32</sup>

EXPERIMENT 3.—Four rats were given eleven, thirteen, twenty and twenty-three subcutaneous injections, respectively, of 2 cc. of a 1 per cent solution of trypan blue, one injection every two days. At the same time 0.1 cc. of a 20 per cent solution of potassium iodide was injected into the right humero-ulnar and femorotibial joints in order to produce a mild inflammation of the synovial membrane.<sup>33</sup>

The changes in the joints on the left side were similar to those detailed in the report of experiment 1. The animals which had received twenty or twenty-three injections of trypan blue showed more dye in articular tissues than any in the series previously described. The histiocytes were much enlarged. The cytoplasm was so crowded with granules of trypan blue that the individual vacuoles were often invisible. Some cells were almost black. The shape of the cells was altered because of the large number and the crowding of the cells. The fibrocytes contained an unusually large amount of the dye in granules and short rods. Considerable dye was seen in the bone marrow. Numerous histiocytes containing trypan blue were scattered among the fat cells of the articular fat pad, and many were seen in the intermuscular septums. Less trypan blue was seen in the humero-ulnar joint than in the femorotibial joint.

In contrast, the joints from the right side, into which had been injected a 20 per cent solution of potassium iodide in order to produce a mild inflammatory reaction, showed even more trypan blue than the joints on the left side. The histiocytes were so full of the dye in many instances that the cytoplasm was completely obscured. The joints showed rather extensive proliferation of the synovial membrane, with a great increase of the folds or villi, and it was in these folds that the largest amount of trypan blue was noted. In a number of places the epithelioid layer of connective tissue cells was much thickened with parallel layers of histiocytes.<sup>34</sup> There was a great increase in the number of fibrocytes, and the blood vessels appeared to be considerably engorged.

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32. Herring, P. T., and MacNaughton, F. G.: *Lymphatics and Lymph Glands*, *Lancet* **1**:1081, 1922.

33. Cameron, D. F.: *A Comparative Study of Sodium Iodide as an Opaque Medium in Pyelography*, *Arch. Surg.* **1**:184 (July) 1920.

34. It is well known from the classic studies of J. A. Hammar (*Ueber den feineren Bau der Gelenke*, *Arch. f. mikr. Anat.* **43**:266, 1894) and H. Braun (*Untersuchungen über den Bau der Synovialmembranen und Gelenkknorpel, sowie über die Resorption flüssiger und fester Körper aus den Gelenkhöhlen*, *Deutsche Ztschr. f. Chir.* **39**:35, 1894) and also from the recent full descriptions by J. A. Key (*The Synovial Membrane of Joints and Bursae*, in Cowdry, E. V.: *Special Cytology*, New York, Paul B. Hoeber, Inc., 1932, vol. 2) and L. A. Sigurdson (*The Structure and Function of Articular Synovial Membranes*, *J. Bone & Joint Surg.* **12**:603, 1930) that articular cavities are lined by connective tissue, the branched cells being arranged in a single layer or layers several cells deep. From their reactions toward certain injected dyes these cells may be identified chiefly as histiocytes and fibrocytes.

The findings suggest that a local inflammatory response causes a greater deposition of trypan blue.<sup>35</sup> It is impossible, however, to measure the amount of dye present in a joint. Whether the apparent increase in trypan blue in a joint into which repeated injections of potassium iodide have been made is the result of an increased local proliferation of histiocytes<sup>36</sup> or an increased migration from without cannot be determined. Occasional mitotic figures are seen in histiocytes. Fibrocytes in the synovial membrane rarely show mitoses.<sup>37</sup> Previous observers<sup>38</sup> have found increased deposition of substances in tissues in inflammation. The experiments of Böhm<sup>39</sup> and others suggest that a mild inflammation stimulates the local activity<sup>40</sup> of the reticulo-endothelial system, while a severe inflammatory response depresses it.<sup>41</sup>

EXPERIMENT 4.—In a series of four rats a blow sufficient to produce swelling for several days was struck directly on the right femorotibial joint. This was repeated twice weekly, and at the same time subcutaneous injections of 2 cc. of a 1 per cent aqueous solution of trypan blue were made. The animals received six, eleven, thirteen and twenty-one injections, respectively. At necropsy both humero-ulnar and femorotibial joints were removed.

The microscopic picture was similar to that described before. In the joints on the right side, which had been subjected to repeated trauma, there appeared to

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35. This increased deposition of trypan blue is probably the combined effect of inflammatory changes and those induced by the injection of a potassium salt. K. Sato (On the Real Nature of Vital Staining, *Folia anat. japon.* 8:51, 1929) observed increased intra-vitam accumulation of dyes following injection of potassium salts. It was suggested by F. Grossman (Ueber das Verhalten der Leberzellen bei vitaler Speicherung, *Frankfurt. Ztschr. f. Path.* 36:635, 1928) that various poisons, perhaps through increasing cellular permeability, facilitate the taking up of trypan blue, india ink and other dyes, and S. Sawelsohn (Untersuchungen über die Speicherung einiger Vitalfarbstoffe in den Leberzellen, *Ztschr. f. Zellforsch. u. mikr. Anat.* 8:602, 1929) described an increment of trypan blue in rats following an injection of arsenic. Both Sawelsohn and G. C. Dogliotti (Ricerche sull'assunzione di trypanblau da parte delle cellule epatiche nei ratti albin, *Monitore zool. ital.* 40:100, 1929) pointed out the importance of the nutritional state of the animal in the intra-vitam storage of dyes.

36. Bauer, K.: Beitrag zur Frage der Makrophogenese im entzündeten Gewebe bei vitalgespeicherten Tieren, *Ztschr. f. Zellforsch. u. mikr. Anat.* 9:155, 1929.

37. Bloom, W.: Some Relationships Between the Cells of the Blood and of the Connective Tissue, *Arch. f. exper. Zellforsch.* 11:145, 1931.

38. Koll, K.: Bindegewebsstudien: II. Die Wirkung von Patentblau auf das Unterhautbindegewebe der Maus, *Ztschr. f. Zellforsch. u. mikr. Anat.* 4:702, 1927.

39. Böhm, A.: Die Funktionsänderung des reticulo-endothelialen Systems bei Infektionen, *Arch. f. Dermat. u. Syph.* 167:74, 1932.

40. Weatherford, H. L.: Chondriosomal Changes in Connective-Tissue Cells in the Initial Stages of Acute Inflammation, *Ztschr. f. Zellforsch. u. mikr. Anat.* 17:518, 1933.

41. Petersen, W. F.; Jaffé, R. H.; Levinson, S. A., and Hughes, T. P.: Studies on Endothelial Permeability: IV. The Modification of Canine Anaphylactic Shock by Means of Endothelial Blockade, *J. Immunol.* 8:367, 1923.



be the same amount of trypan blue as in the joints on the untraumatized side. There was a rather marked increase of connective tissue. No increase or apparent dilatation of the blood vessels was observed. The fibrocytes tended to assume layer-like formations parallel to the synovial surface. As in sections in the previous experiments, there was a tendency on the part of the histiocytes to approach the surface and form an epithelioid layer. In the traumatized joints there seemed to be a much greater accumulation of dye-laden histiocytes in the periarticular tissues than in the joints of the other side.<sup>42</sup> Perhaps with more severe mechanical trauma there would have been sufficient inflammation to cause a noticeable difference in the deposition of dye in the synovial membrane also and even marked decrease in storage, such as Menkin<sup>43</sup> has observed. Fenton and Larsell<sup>44</sup> observed the mobilization of large numbers of histiocytes in the nasal mucous membrane of cats after physical trauma.

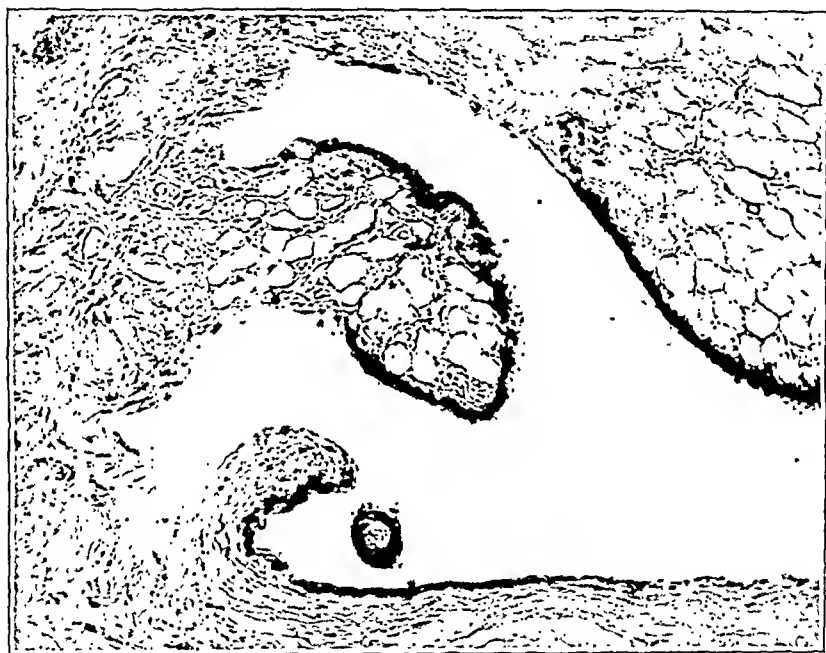


Fig. 3.—Photomicrograph of a knee joint of a rat after twenty subcutaneous injections of trypan blue and repeated trauma to the joint. The dark borders of the articular cavity represent collections of dye-laden histiocytes. The more scattered histiocytes in the periarticular tissue appear lighter.

EXPERIMENT 5.—In four rats the right sciatic nerve was cut in the upper third of the thigh in order to produce paralysis of the muscles of the foot. This was followed as soon as the animal had recovered from the operation by subcutaneous

42. Carscadden, W. G.: Early Inflammatory Reactions in Tissues Following Simple Injury, *Arch. Path.* 4:329 (Sept.) 1927.

43. Menkin, V.: Studies on Inflammation: VIII. Studies on the Fixation of Urea; a Further Study on the Mechanism of Fixation by the Inflammatory Reaction, *J. Exper. Med.* 56:151, 1932.

44. Fenton, R. A., and Larsell, O.: Reticulo-Endothelial Components of Accessory Sinus Mucosa, *Arch. Otolaryng.* 14:586 (Nov.) 1931.

injections of 2 cc. of a 1 per cent solution of trypan blue twice weekly. The animals were given ten, thirteen, fourteen and fifteen injections, respectively. The tarsal and ankle joints on both sides were removed for microscopic study the day after the last injection.

The microscopic appearance of the tarsal joints of the unparalyzed side was similar to that observed in the previous experiments. On the paralyzed side there was considerably less dye in the synovial membrane and in the periarticular tissues. Raszeja<sup>26</sup> observed a lessened deposition of trypan blue in immobilized knee joints of rabbits. The decreased deposition of dye in the paralyzed joints was probably the result of inactivity because of the paralysis, the accompanying local impaired circulation and lessened metabolic conditions.

EXPERIMENT 6.—In an attempt to produce a local blocking of the reticulo-endothelial system, repeated injections of india ink were made into the right femorotibial and humero-ulnar joints. Nine injections of 0.1 cc. were given twice

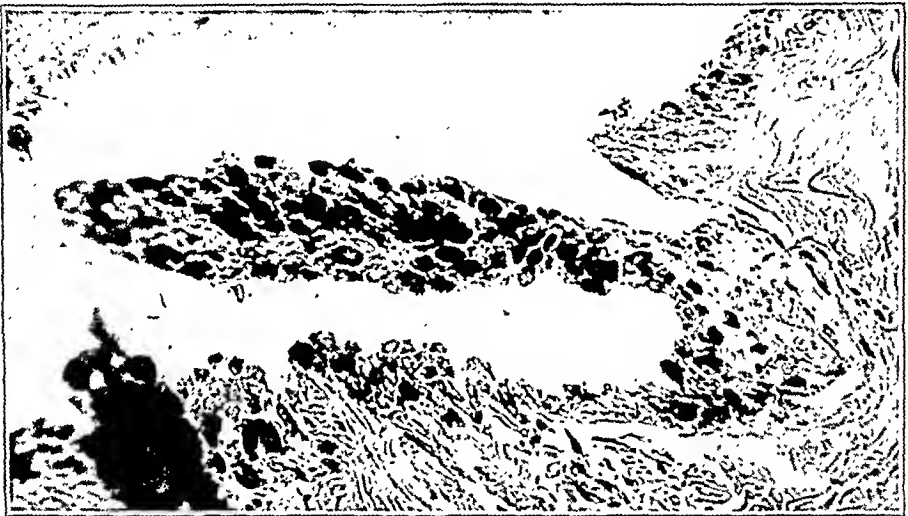


Fig. 4.—Photomicrograph of a knee joint of a rat after nine intra-articular injections of india ink and nine subcutaneous injections of trypan blue. The histiocytes are greatly engorged with particulate matter, chiefly ink. The particles of ink obscure those of trypan blue.

a week to each of four animals. Subsequently biweekly injections of 2 cc. of a 1 per cent solution of trypan blue were made subcutaneously two, nine, thirteen and fourteen times, respectively.

Microscopic study of the joints from the right side showed many carbon particles on the surface of the synovial membrane, some enmeshed in fibrin. Many histiocytes containing much india ink were seen just beneath the surface of the synovial membrane. Trypan blue either was present in lesser quantity in the histiocytes or was masked by the india ink. There was a moderate proliferation of the synovial membrane.

The observations in this experiment on the whole were meager. No definite conclusions can be drawn as to the local ability of the tissues to pick up and store trypan blue. The sections from the joints on the left side, into which no india ink had been injected, showed the usual

amount and location of trypan blue. Other investigators<sup>45</sup> have observed lessened absorption of injected substances by the reticulo-endothelial system after local or systemic injections of materials which must be handled by this system. Such depression of phagocytic activity, the so-called endothelial blockade,<sup>46</sup> is temporary, and the material, unless entirely inert or extremely irritating, is soon removed from the body.

EXPERIMENT 7.—A further attempt was made to block the reticulo-endothelial system by the intra-articular injection of oil. Twelve biweekly injections of 0.2 cc. of liquid petrolatum were made into the left femorotibial joint of six rats. Biweekly injections of 2 cc. of a 1 per cent solution of trypan blue were then given subcutaneously ten, eleven, twelve, fifteen and eighteen times, respectively. At necropsy both humero-ulnar and femorotibial joints were removed.

Studies on the removal of oily substances from tissues have shown that the oil is taken up in tiny globules by phagocytic cells, chiefly by histiocytes.<sup>47</sup> Pinkerton,<sup>48</sup> in his experiments on the reaction of the bronchioles and alveoli of the lungs to injected oils, found that there was a less vigorous inflammatory response to a hydrocarbon-like liquid petrolatum. In our animals the humero-ulnar joints and the right femorotibial joint contained trypan blue in the synovial membrane much like that shown in the previous experiments. In the left femorotibial joint there was moderate synovial proliferation. A little oil was seen in the joint cavity. A small amount in tiny globules in histiocytes was present superficially in the synovial membrane. The amount of trypan blue present in the synovial membrane was apparently about equal on the two sides.

This experiment suggests that a definite local blocking of the reticulo-endothelial system against the phagocytosis of trypan blue cannot be produced by an oil of low toxicity, like liquid petrolatum. Oils, e. g., olive oil, were used extensively in the mobilization of stiffened joints by Baer<sup>49</sup> and others, but their use was discontinued because fibrosis and increased stiffening of the joints resulted. Liquid petrolatum is absorbed slowly when injected into tissues, as numerous observers have found, but the rate and amount of absorption are not sufficient to produce a noticeable local change in the function of the reticulo-endothelial system.

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45. Acqua, G. D., and Strauss, W.: Blockade des reticulo-endothelialen Systems, *Klin. Wchnschr.* **12**:1935, 1933.

46. Thomoff, Z.: Influence du blockage du système réticulo-endothélial sur le phénomène de Koch et sur l'intradermoréaction tuberculinique chez les cobayes, *Compt. rend. Soc. de biol.* **110**:168, 1932.

47. Nolasco, J. O.: Lymphatic Absorption of Oily Antileprotic Drugs, Given Intradermally and Subcutaneously, *J. Philippine Islands M. A.* **12**:147, 1932.

48. Pinkerton, H.: The Reaction to Oils and Fats in the Lung, *Arch. Path.* **5**:380 (March) 1928.

49. Baer, W. S.: Some Observations on the Use of Oil in the Mobilization of Joints, *Am. J. Orthop. Surg.* **5**:234, 1907.

EXPERIMENT 8.—Two rats were given 8 cc. of a 2 per cent solution of trypan blue by stomach tube intragastrically twice weekly seven and fourteen times, respectively. The dye was apparently well tolerated by the gastro-intestinal tract; the animals remained in good health and ate heartily. There was slight blue staining of the feces. The animals slowly became blue, but the staining of the skin was much less than in any of the rats receiving an equal number of injections subcutaneously.

Necropsy showed marked staining of the lower end of the esophagus and the stomach. The staining of the intestinal tract was less and faded out entirely when the transverse colon was reached. The mesenteric lymph nodes were stained a deep blue. There was a moderate amount of blue staining of the diaphragm, liver, spleen and kidneys. The femorotibial joints showed a moderate deposition of trypan blue, chiefly in histiocytes, which was similar to that seen in the previous experiments. In no case was this equal to the amount observed after subcutaneous injections.

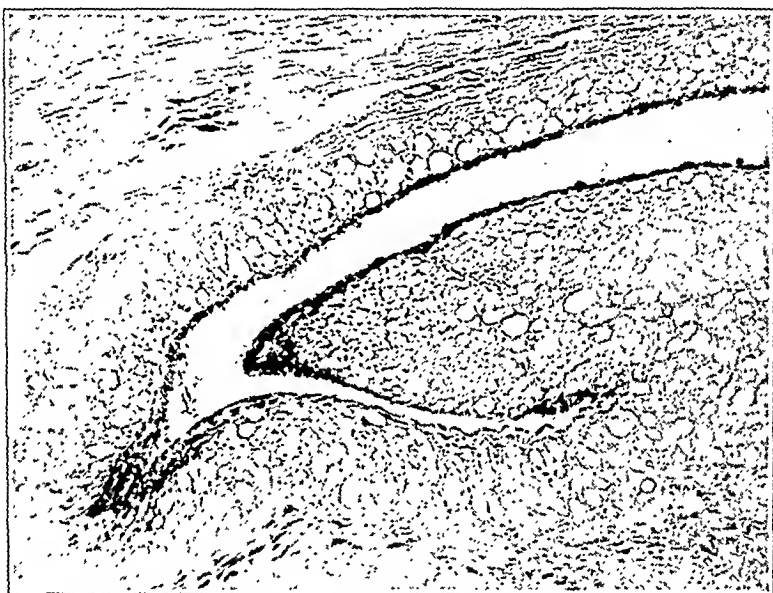


Fig. 5.—Photomicrograph of a knee joint of a rat after twelve intra-articular injections of liquid petrolatum followed by twelve subcutaneous injections of trypan blue. A moderate amount of dye is present in histiocytes, chiefly in the superficial parts of the synovial membrane. A number of histiocytes appear vacuolated.

This experiment showed that deposition of trypan blue in reticulo-endothelial cells around the joints can occur after absorption of dye through the gastro-intestinal tract. Apparently a longer time is required and greater amounts of dye are necessary to produce a demonstrable deposition in the synovial membrane. It is well known that trypan blue given orally is not absorbed readily at first but that later, after considerable damage has been done to the mucosa of the gastro-intestinal tract, marked absorption takes place. There are numerous clinical

observations that certain foodstuffs in large amounts or with improper metabolism can lead to pain<sup>50</sup> and swelling in joints. We have proof in gout of the harmful effects of excessive purine intake by the deposition of urates about articular cavities. Fletcher and Graham,<sup>51</sup> Lane,<sup>52</sup> and Osgood<sup>53</sup> have observed disturbances in joints apparently associated with faulty elimination from the body.

The study of the joints from our animals shows how readily particulate matter can be taken up from subcutaneous tissues or from the gastro-intestinal tract. Several stages of phagocytosis, with carriage chiefly through the blood stream, were probably required before the ultimate deposition of the matter in articular tissues. Subsequent removal of at least the larger amount of the dye, with eventual excretion from the body, would undoubtedly have taken place if sufficient time had been given. How much harm could have been done to the joint in the temporary storage of more irritating substances can only be conjectured.

The reticulo-endothelial system in its relation to joints becomes of more than academic importance when one considers that materials of greater than molecular size, bacterial toxins or metabolic products, can be carried through the blood stream to articular cavities from the superficial tissues and from the gastro-intestinal tract.<sup>54</sup> Materials given by injection in the treatment of arthritis which do not remain in solution are removed from the tissues and the circulating blood by this aggregation of phagocytic cells. The fact that in our animals distribution and storage of trypan blue were less in articular tissues than in other tissues, especially hepatic and renal, leads one to question how effective many of the solutions of intricate molecular composition and the great number of colloidal preparations used parenterally for diseases of the joints really are as local bactericidal agents or metabolic stimulants. One supposes that their only therapeutic efficacy is due to a stimulation of the reticulo-endothelial system.<sup>55</sup>

Bacteria and other substances absorbed from various tissues usually are brought to joints after passing through the liver. This organ

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50. Cummings, F. A.: The Colon as a Focus of Infection, *Rhode Island M. J.* **17**:1, 1934.

51. Fletcher, A. A., and Graham, D.: Large Bowel in Chronic Arthritis, *Am. J. M. Sc.* **179**:91, 1930.

52. Lane, W. A.: Chronic Intestinal Stasis, *Lancet* **2**:1706, 1912.

53. Osgood, R. B.: Etiologic Factors in Certain Cases of So-Called Sciatic Scoliosis, *J. Bone & Joint Surg.* **9**:667, 1927.

54. Ratner, B., and Gruehl, H. L.: Passage of Native Proteins Through Normal Gastro-Intestinal Tract, *J. Clin. Investigation* **13**:517, 1934.

55. Forestier, J.: Rheumatoid Arthritis and Its Treatment by Gold Salts, *Lancet* **2**:646, 1934.

probably plays the part of intermediary in the carriage of all toxic substances to articular tissues from the gastro-intestinal tract. Whether noxious substances reach joints only when they are brought in too large quantities or when the functional activity of the liver is impaired, we do not know. In certain parts, e. g., the extremities, particulate matter can be transported to joints without passage through the liver. The passage of bacteria or toxins may occur in this manner from foci of infection.<sup>56</sup>

Our study shows the common mechanism for the removal of material from tissues of the body and from the gastro-intestinal tract and the manner in which such material can be stored about articular cavities. All the evidence suggests that bacteria and toxins not in solution may be carried in the same way. What relation bacteria or toxins stored in articular tissues by the reticulo-endothelial cells may have to the evolution and continuation of the various arthritides is only partially answered by clinical investigation.<sup>57</sup> That many bacteria are destroyed within histiocytes is well known.<sup>58</sup> It is equally well known that other bacteria multiply intracellularly and eventually destroy the phagocytic cell.<sup>59</sup> Tuberculosis of joints in all probability occurs in this manner. A number of investigators have reported the isolation of bacteria from joints involved by chronic arthritis.<sup>60</sup> As to so-called toxins, we believe that they exist and that they may arise from foci of infection and from the gastro-intestinal tract, but such substances have not been isolated or recovered from articular cavities. Experimental studies have shown that many substances introduced into the articular cavity can produce inflammation of, and injury to, joint tissues.<sup>61</sup>

The important question and one still unsolved is: How can one use the reticulo-endothelial system in the therapy of articular diseases? Knowledge is still too fragmentary to offer any definite leads for the

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mechanical or pharmacologic stimulation of this system.<sup>62</sup> Nissen<sup>63</sup> has shown that injections of protein in small doses stimulate it, and Soper<sup>64</sup> has observed a similar effect with small doses of roentgen rays. Depression of the function of the reticulo-endothelial system in order to prevent the carriage of substances to joints would scarcely be possible, nor might it be desirable. But if one can stimulate it,<sup>65</sup> in order to secure more efficient removal of bacteria or inflammatory products and tissue debris, and in addition bring about the more abundant production of intracellular antistances<sup>66</sup> against toxins or bacteria,<sup>67</sup> a definite advance will have been made in the treatment of articular diseases.

#### CONCLUSIONS

1. Colloidal and particulate matter is carried to articular cavities from the various tissues of the body, such as the skin and the gastrointestinal tract, through the blood stream.

2. Such transported material is stored chiefly in histiocytes in the synovial membrane. Large amounts are stored in the bone marrow. Lesser amounts are seen in the intermuscular septums and in the articular fat pads.

3. Mild inflammation in articular tissues tends to increase the amount of deposition of such transported substances.

4. Local blocking of the reticulo-endothelial system is transitory and incomplete and is ineffective in preventing the deposition of colloidal and particulate matter in articular tissues.

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## INFLUENCE OF MOTION ON HEALING OF FRACTURES

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OAK PARK, ILL.

In a recent study of the rôle of the hematoma<sup>1</sup> in healing fractures it was shown that bony callus grew readily into a blood clot placed over a slight defect in the radius of a dog. As a result of these studies it seems warranted to state that the hematoma serves an important function in the formation of bony callus: as an indifferent base, a trellis, for the ingrowth of callus; as an irritant, stimulating the rapid development of hyperemia and the formation of new capillaries; as a medium for the retention of a possible enzyme influencing the deposition of calcium salts and the development of osteoid tissue, or as a defense wall against the ingrowth of connective tissue. More than likely all these factors come into play in the complex process of the formation of new bone.

The fragments of a broken bone incapable of producing or utilizing the stimulus for repair by new bone are eventually united by scar tissue. Fibrous tissue is the least differentiated structure in the body, and it usurps every space not occupied by a more specialized growth. It may properly be termed invasive *connective tissue*. The only highly differentiated structures in the body which repair themselves with like cells are osseous, epithelial and glandular tissues. All others are repaired by scar tissue, which serves the purpose of joining structures and filling in space. The aim of treatment for fracture is to keep out fibrous tissue while bone is being repaired by bone. In case of delayed union scar tissue invades the space between the fragments; in case of nonunion the fibrous tissue completely covers the ends of the fragments and renders them incapable of stimulating further bony repair—the bone-growing impulse has been choked. Whenever for some reason new bone cannot rapidly fill in the gap between fractured surfaces, connective tissue bridges the defect.

This paper is a brief report of an experimental study of the ingrowth of fibrous tissue into the line of fracture in the presence of slight motion.

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## EXPERIMENTAL WORK

In the first series of experiments dogs were employed; the radius was sawed completely across with a saw 1 mm. wide, the point of division being in the midportion of the bone. The muscles were loosely closed with a few sutures and the cutaneous edges approximated with fine subcuticular catgut; no dressing was applied. No infections occurred. (In earlier experimental work on dogs, in which the wounds were closed with through and through skin stitches, infections occurred rather regularly.)

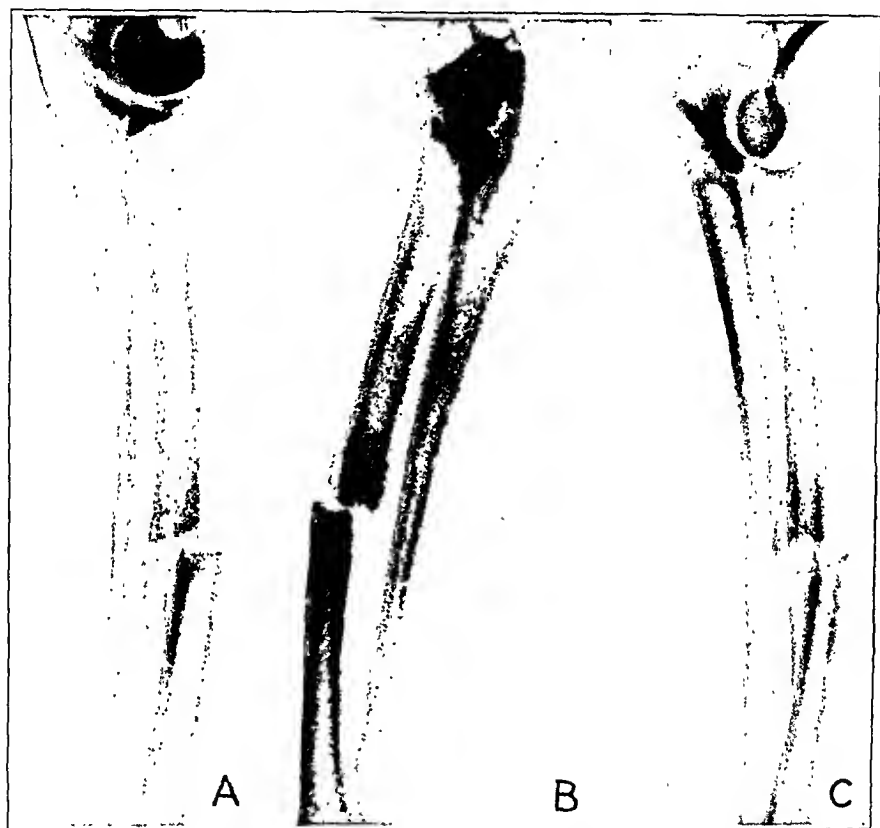


Fig. 1.—Roentgenograms of fractures taken at various intervals after operation. *A* (dog 7), thirty-eight days after operation, shows about 50 per cent apposition of the fragments, considerable growth of callus along the inner side of the lower half of the radius and a moderate amount of callus on the outer side of the upper portion of the radius. *B* (dog 8), sixteen days after operation, shows a callus on the medial side of the lower fragment and the lateral side of the upper fragment. *C* (dog 8), thirty-seven days after operation, shows still more distinctly how the callus has grown along the sides of the shaft of the bone in the protected areas and how the masses of bony callus have approached the ends of the fragments but have not bridged them.

Roentgenograms were made at various intervals. After from forty to sixty-five days the animals were killed, and the bones were removed, cleaned and cut for microscopic study. Only a few, characteristic protocols will be outlined.

Dog 7.—On January 12 the left radius was sawed across. A roentgenogram (fig. 1 *A*) taken on February 19, thirty-eight days after the operation, showed

about 50 per cent apposition of the fragments, marked growth of callus along the inner side of the lower half of the radius and a moderate amount of callus on the outer side of the upper portion of the radius. The callus had formed primarily in the areas protected by the overhanging bone, where the blood clot had been undisturbed and immobile. The entire callus lay outside the periosteum, which had been painstakingly neither raised nor injured during the operation. The feature most pertinent to this discussion was the observation of a definite transverse line at the point of apposition of the fragments, where the roentgenogram showed no bony callus. The line was noted at the only possible point of motion. That there was some motion was assumed because the animal walked about on the leg almost immediately after the operation. The dog was killed forty-two days

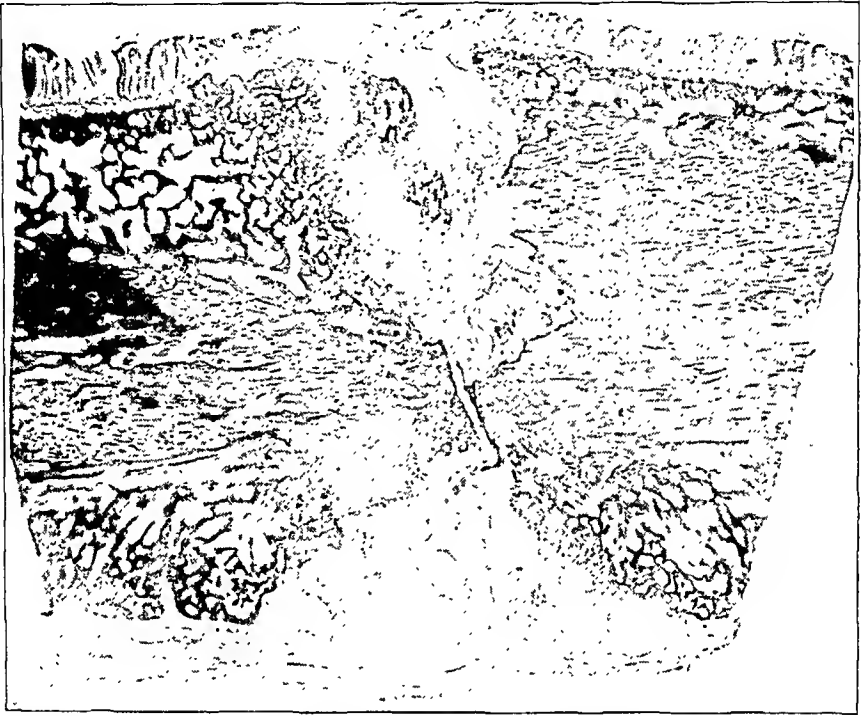


Fig. 2. (dog 8).—Photomicrograph showing large masses of new bone on the sides of the shaft and a definite line of fibrous tissue still present between the fragments after sixty-five days.

after operation. The specimen which was removed showed a definite fibrous union, and microscopic examination confirmed this observation.

Dog 8.—On January 13 the radius was saved completely across. A roentgenogram (fig. 1 *B*) taken on January 29, sixteen days after the operation, showed a callus on the medial side of the lower fragment and the lateral side of the upper fragment; in each instance the callus lay in the protected areas and, interestingly, not over the ends of the bone. Another roentgenogram (fig. 1 *C*), taken on February 19, thirty-seven days after the operation, emphasized still more distinctly how the callus had grown along the sides of the shaft of the bone in the protected areas and how these masses of bony callus had approached the ends of the fragments but had not bridged them.

The dog was killed on March 15, sixty-five days after the operation. The radius, which was removed and cleaned of all muscle, showed a large mass of callus completely surrounding the ends of the bone. However, motion between the fragments was possible.

Microscopic examination (fig. 2) showed large masses of new bone on the sides of the shaft and a definite line of fibrous tissue still present between the fragments after sixty-five days. In the center of this fibrous tissue lay an island of new bone. The masses of callus on the sides were approaching each other but were separated by a large triangular area of fibrous tissue.

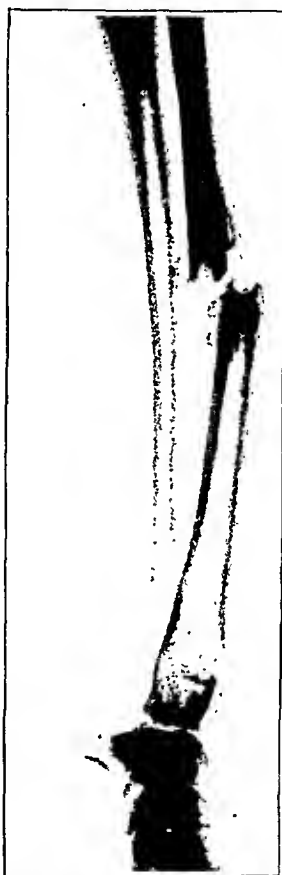


Fig. 3 (dog 11).—Roentgenogram forty-three days after the operation, showing triangular masses of callus in the protected areas at the side of the shaft.

DOG 11.—On January 20 the radius was sawed entirely across. In the roentgenogram (fig. 3) taken forty-three days later, on March 4, there were noted, as in the previous experiments, triangular masses of callus in the protected areas at the side of the shaft; the bases of the triangles extended toward the ends of the opposing fragment.

On March 15, fifty-five days after the operation, the animal was killed and the radius was removed. Grossly, the fragments were firmly welded together, but motion was still possible at the point of the section.

A microscopic examination (fig. 4) confirmed strikingly what was shown roentgenographically. Since the ends of the bone did not lie in the same plane, the microscopic section was approximately of the center of the proximal fragment and of the very edge of the lower fragment. New bone in irregular masses, laid down in nondescript fashion, was observed in the protected areas along the shaft. The new bone had filled the space where the blood clot lay undisturbed and where, presumably, that something which is undoubtedly released—an enzyme?—when the bone is injured could be kept in contact with the ingrowing capillaries and influence the deposition of calcium salts and their transformation into bone.

A definite layer of fibrous tissue, the strands running transversely to the shaft of the bone, occupied the space between the fragments. This fibrous tissue had grown from without inward. The upper fragment was entirely covered with

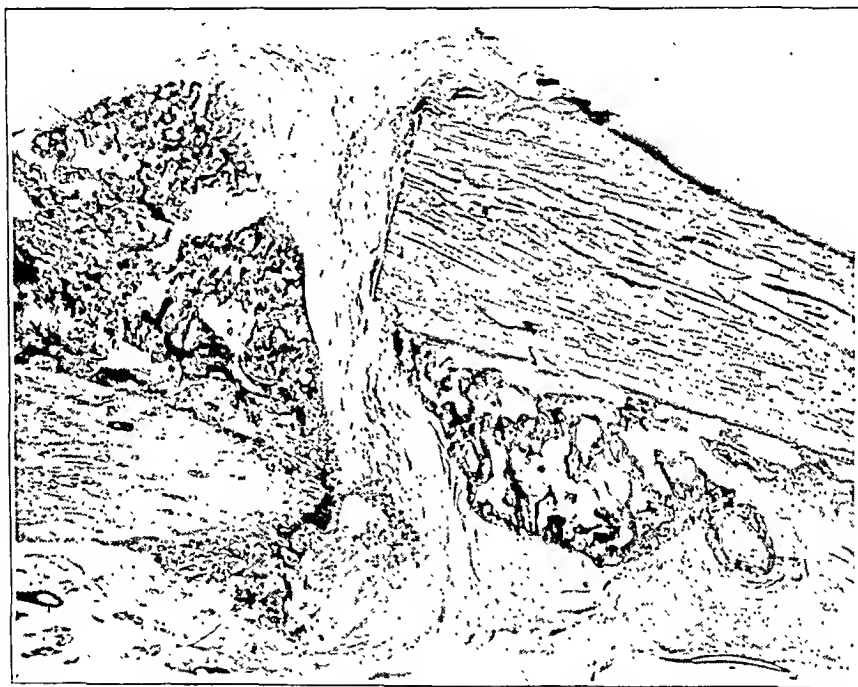


Fig. 4 (dog 11).—Photomicrograph confirming roentgenologic observations.

adult scar tissue, firmly plastered against the ends of the bone. The stimulus to callus formation must have come from the injured bone, and yet the callus lay not at the ends of the fragments but at the sides of the shaft. The point of motion was necessarily between the ends of the fragments and interfered with the formation of osteoid tissue but not with the growth of connective tissue.

Of the other six animals used, each showed in varying degree what is set forth in the foregoing protocols. A voluminous callus was noted in each animal, fifty-nine, fifty-four, forty-eight, fifty-five, thirty-five and forty-eight days, respectively, after the fracture, but definite motion between the fragments was still possible. It is, of course, recognized

that eventual bony union would have resulted in each instance, because nonunion following simple fracture does not occur in the experimental animal.

To prove that motion was the sole factor in the development of the band of fibrous tissue between the fragments of bone, a second series of experiments was done, under exactly the same conditions except that the bone was sawed only half-way across. The bone remained rigid,



Fig. 5 (dog 18).—Roentgenogram confirming gross observations. The cut in the bone is still visible but is filled with bone, and the callus over the defect is a typical heterogeneous new bone.

but the stimulus to callus formation was present. Twelve animals were used, and all showed in varying degree what will be described in one characteristic protocol that follows:

Dog 18.—On February 12 the left radius was sawed half-way across. The periosteum was uninjured except at the point of cutting. A blood clot was allowed to form over the defect in the bone, and the muscles were loosely closed

so as not to dislodge it. On April 12, fifty-nine days after the operation, the animal was killed, and the left radius was removed. There was a large callus, 1.5 cm. long and 3 mm. high, lying over and completely bridging the defect in the radius. The callus was greatest directly over the cut. A roentgenographic examination (fig. 5) confirmed the gross observations. The cut in the bone was still visible but was filled with osseous tissue, and the callus over the defect was typical heterogeneous new bone.

A microscopic examination (fig. 6) confirmed the results of the gross examination. The fragmentation was due to the fixative process. The new bone filling the defect was continuous with that lying on the shaft. The old periosteum of the shaft had been absorbed or ossified, and a new layer of periosteum had formed over the mass of callus. The stimulus for the growth of this mass of new bone 1.5 cm. long over a defect 1 mm. wide could have come only from the minor injury to the bone.

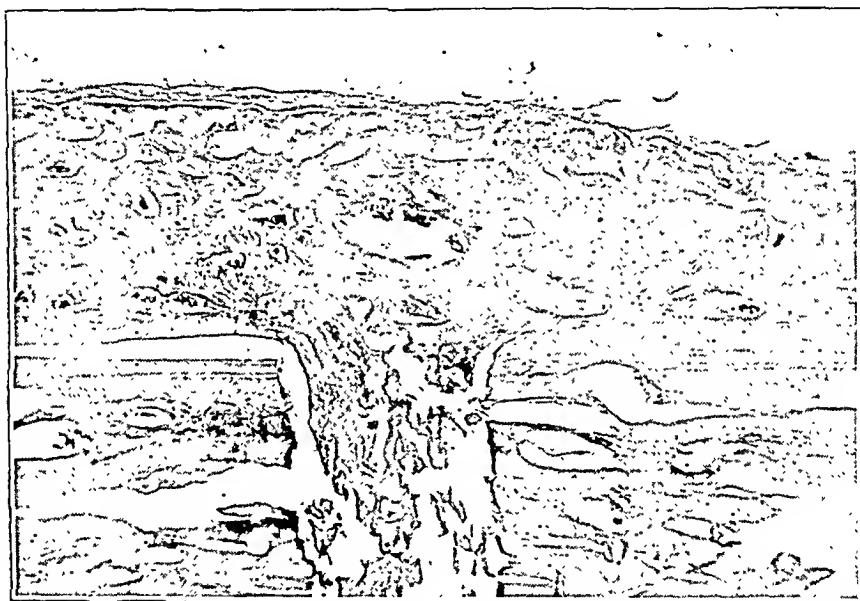


Fig. 6 (dog 18).—Photomicrograph confirming gross observations. The fragmentation was due to the fixative process.

#### COMMENT

When a fracture occurs there is damage to more than one tissue. Each responds to the stimulus to repair. In the vast majority of instances the injured periosteum, cortex and endosteum furnish amply the necessary stimulus to cause the deposition of calcium salts, their transformation into osteoid tissue and, finally, their formation into new bone. If conditions are not right—for example, when the periosteum has been pulled off or destroyed or the blood supply is deficient or the bone sclerotic—scar tissue gains the upper hand and, because of its

low differentiation and greater power of growth, fills in the space before the elements that cause the regeneration of bone can do so.

Nonunion is more common after a transverse than after an oblique or spiral fracture. One would expect this for two reasons. First, in the latter type there is more raw bone surface and, consequently, more stimulation toward callus formation; second, the greater the area of opposing raw bone surfaces, the less the opportunity for connective tissue to crowd in before regeneration of the bone has established itself.

Bone is a rigid structure, differing in this respect from all other tissues. It seems reasonable to suppose that for the repair of such a rigid structure immobility is essential. If there is movement in the mold as a cement block hardens, a weak spot will result; if there is motion between freshly broken ends of bone the newly solidifying callus will break, and if this trauma is repeated often enough, fibrous tissue will grow in. Fortunately, the stimulus to healing of bone is usually sufficient to overcome many handicaps to its repair. A fracture in a child practically always heals; in an adult, a fracture at the end of a long bone, such as the upper or the lower ends of the tibia or the lower end of the humerus, radius or femur, practically never fails to unite. In a fracture about a joint, where the bone is cancellous and the blood supply is good, healing occurs regardless of mobility and often with excessive callus, while in a fracture of the middle third of the humerus, the tibia or the radius, where the bone is sclerotic and the blood supply uncertain, there is always the danger of nonunion. Buresch<sup>2</sup> designated as "a pathological axis" that point in the mid-portion of a long bone where the muscles, acting on the fragments, produce motion of the fractured surfaces on each other, with a consequent pseudarthrosis. Besides accurate reduction, Böhler<sup>3</sup> emphasized the importance of continuous, uninterrupted fixation until healing occurs. To this end he has long advocated the unpadded cast, claiming that a heavily padded cast allows too much motion and promotes nonunion. During the healing process he advised activity of as many joints of the extremity as possible, as well as movement of the entire body but as absolute a fixation as possible of the fractured surface. Bum<sup>4</sup> said: "Keep the bones still but the muscles active."

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## CONCLUSION

This series of experiments demonstrates:

1. The profuse growth of callus in the protected area about any point of injury to the bone.
2. The ingrowth of fibrous tissue between the fragments of bone at the point of motion.
3. The rapid and complete bridging of a defect in the bone in the presence of complete immobilization.

The stimulus of function in old poorly healing fractures is quite another story.



# CYSTS OF THE SEMILUNAR CARTILAGES

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AND

M. B. SHAW, M.D.

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Cysts of the menisci of the knee joint are of sufficient rarity that we wish to present the 4 cases that we have observed and summarize the material collected from the available literature. We have been able to find 159 case reports, making a total of 163 cases described to date. All authors are agreed on the symptomatology, the signs and the treatment, but there is some difference of opinion as to the etiology. We shall discuss the points of agreement and dissension and then present our cases.

Nicole in 1933 was able to collect reports of 127 cases from the literature. We have found reports of 36 additional cases, including our own. In 23 of these 163 cases the cyst was in the medial meniscus and in 104 in the lateral meniscus. In 36 cases the site was not stated. One case of bilateral cyst was reported by Majer. The right knee was involved in 43 instances and the left in 33, the leg not being differentiated in 87 cases. Of the 163 patients, 76 were males and 25 females; in 62 cases the sex was not stated.

## SYMPTOMS

Typically the patient with a cyst of the meniscus is a young adult who has suffered aching pain or has noted a mass in the region of the knee. Of the 33 cases in which the principal complaint was noted, pain was outstanding in 16 and the presence of a mass in 17. The duration of symptoms varied from seven days to ten years in the 40 cases in which this feature was recorded.

A frequent complaint was easy fatigue of the affected limb. In only a few instances did the condition cause a limp or limit the motion of the knee joint.

Trauma was noted in 23 cases, while in 29 cases no injury was known to have occurred. In the other 110 cases this particular factor was not reported. Heusser stated that 50 per cent of patients gave a history of injury. There is no similarity in the types of trauma, which range from slight twists to severe "clipping" injuries sustained in football.

The onset of symptoms is insidious. The pain may be aching or sharp, and it remains a constant feature, while the tumor rather rapidly reaches a maximum size and then remains stationary. The pain may radiate up or down the leg but is always readily localized in the affected area. No cases have been reported in which there was pain but no gross mass on examination and microscopic section showed a cyst. This is a curious fact, because one would think that occasionally a cyst would be discovered incidentally among the hundreds of cartilages removed each year for other reasons.

*Available Case Reports*

Year	Author	No. of Cases	Year	Author	No. of Cases
?	*Allingham.....	1	1929	Nové-Josserand.....	1
1883	Nicaise.....	1	1929	Venezian.....	1
1898	Kummer.....	1	1929	Campbell and Mitchell.....	9
1904	Edner.....	1	1929	Delchef.....	2
1906	Schmidt.....	1	1929	Silverskiöld.....	2
1910	Kroiss.....	1	1929	*Auvray.....	3
1911	*Eden.....	2	1929	Tobler.....	3
1914	Riedel.....	5	1930	Zäch-Christen.....	4
1920	Hammer.....	1	1930	Follhasson.....	1
1920	Jastram.....	1	1930	Elmslie.....	1
1921	Ollerenshaw.....	4	1930	*Watson.....	13
1921	*Funrall.....	2	1930	Pouzet.....	1
1923	Phemister.....	2	1931	Mandl.....	2
1924	Jean.....	3	1931	Pyle.....	1
1925	von Gaza.....	1	1931	Dunn.....	3
1925	*Hinrichsmeyer.....	1	1931	Krapf.....	1
1925	Tavernier.....	1	1932	Orr and Heggie.....	1
1926	Oudard.....	1	1932	Marique.....	1
1926	Allison and O'Connor.....	3	1933	Nicole.....	4
1926	Pelizaesus.....	2	1933	Colonna.....	1
1926	*Pels Leuden.....	1	1933	Burman and Sutro.....	6
1927	Majer.....	9	1934	Sorrel.....	1
1927	Kleinberg.....	1	1935	Taylor.....	4
1927	Zadek and Jaffe.....	1		Royal College of Surgeons, museum specimens.....	6
1927	*Edinglors.....	1		Records of St. Bartholomew's Hospital.....	2
1927	Edington.....	1		Records of the Royal National Orthopaedic Hospital.....	1
1927	Nutter and Blew.....	1	1936	Bennett and Shaw.....	4
1928	Heusser.....	3			
1928	Bristow.....	11			
1928	Pandalal.....	1			
1929	Ollerenshaw.....	18			
	Total.....				163

\* Cited by Nicole.

PHYSICAL EXAMINATION

The general physical examination throws no light on the local condition. No pathognomonic physical type or associated general physical signs are noted. Rheumatic fever and syphilis were reported in only a single instance. No cysts were reported in arthritic patients, though popliteal cysts and other synovial outpouchings are common in this condition. Neoplasms have not been associated with this lesion. Ganglions of other locations are not noted to be concomitant with this tumor. Caan reported a ganglion of the cruciate ligaments, not associated with a meniscal cyst, however.

The mass varies in size from that of a hazelnut, or roughly 1 by 1 cm., to that of a large hen's egg, or 3 by 4 by 5 cm. It is tense,

rather firm or semifluctuant, sometimes rubbery in consistency. Tenderness is elicited only on deep pressure. The tumor is frequently noted to vary in size in different positions of the knee, usually enlarging on extension and decreasing on flexion, though the reverse may sometimes obtain.

No signs of local heat or redness have been reported.

The mass appears along the attachment of the anterior third of the cartilage and presents over the anterolateral or anteromedial aspect of the head of the tibia. It has been frequently noted that the mass feels as though attached to this portion of the bone. Most cysts are firmly fixed to the underlying structures, but occasionally one is seen which is sessile beneath the subcutaneous tissue.

The lateral, medial and cruciate ligaments are not commonly relaxed, though this depends on whether a previous injury of sufficient severity has been sustained. Certainly cysts per se are not responsible for relaxation. A tear of the affected meniscus was found in only a few cases.

Increase in the amount of synovial fluid was noted in only 2 instances, though no note was made on this point in the majority of cases.

Flexion deformities were observed in 2 cases, 1 of 5 degrees and 1 of 10 degrees. Atrophy of the thigh or calf was rare but was present if associated with much disuse. In 1 case a rubbery crepitus was present on motion.

#### DIAGNOSIS

The diagnosis should not be difficult to make. Differentiation from a bursa arising from beneath the medial and lateral ligaments and true synovial outpouchings from the joint offer the most common problem. Tumors of the same consistency as the cysts arising from skin, subcutaneous tissue, ligaments, bone, cartilage, lymph and blood vessels and nerve elements might cause some doubt, but tumors of these types are rare in this region. Joint mice or a thickened synovial tag could be responsible for a mass in the proper location, but the history and the associated signs would indicate the diagnosis.

A distinction should be made between parameniscal and true cysts of the cartilage, but most writers have not done so. Indeed, in many instances this distinction would be hard to make, as the primary cyst arises from the lateral edge of the cartilage and immediately dissects outward through the capsule, thus being parameniscal in the bulk of its growth.

#### ETIOLOGY

No cause for the growth of cysts of the semilunar cartilages is known. Trauma is held by most authors as the inciting factor. How-

ever, injury is not known to have occurred in approximately half the cases reported. It is also worthy of remark that of the hundreds of cartilages removed each year because of tears, cysts are reported as a concomitant finding in only 3 or 4 cases. Certainly the major traumas are not to be blamed as the inciting factor in the origin of these cysts.

The age of the patient is significant, in that the cysts are most prone to develop in the latter part of the second decade and in the early part of the third decade. This is clearly shown in figure 1. The average age of the 73 patients whose age was stated was 29.6 years.

Most authors have expressed the belief that the course of events in the formation of the cysts starts with trauma and is followed by hemorrhage into the injured area, mucoid degeneration of the hematoma and the fabrication of a pseudomesothelial cyst wall by compression of the surrounding fibrocartilage. This process is thought to represent a more or less acute change. Allison and O'Connor, Nutter and Blew, Colonna, Folliasson, Jean, Jastram, Heusser, Nové-Josserand,

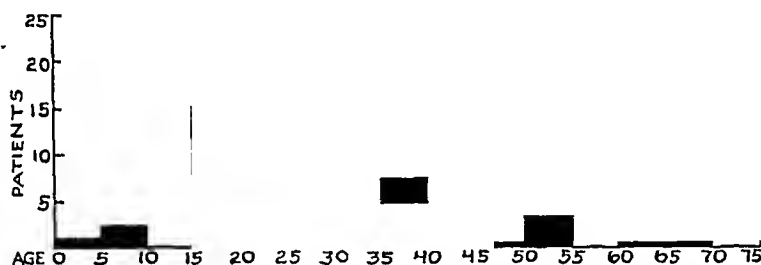


Fig. 1.—Age incidence in 73 cases (average, 29.6 years)

Kroiss, Krapf, Mandl, Orr and Heggie, Pelizaeus, Pyle, Silfverskiöld and Sorrel have indicated that they accept this theory. Another group have said that the process is less acute, that the wear and tear trauma is a more potent factor and that the cysts are identical in nature with ganglions formed in other locations. The formation is, however, dependent on a mucoid degeneration of the fibrocartilage, so that essentially the two theories are not unlike. Bristow, Oudard, Seguy and Dalger, Campbell and Mitchell, Phemister, Fisher, Ebner, Edington, Schmidt, Tobler, Nicole and Thorn have inclined to the latter view.

Taylor has added what would seem to be an astute observation. In his collection of cases he noted that a minor trauma, such as a blow over the attachment of the cartilage, is characteristic in the history. This explains the more frequent occurrence of the cyst in the lateral meniscus and also explains why a history of injury is elicited in less than half the cases. The lateral meniscus is more exposed to blows, and contusions are less likely to be remembered than injuries which

cause gross damage to the cartilage. Taylor has pointed out, too, that the cyst always presents in the most exposed portion of the cartilage, hence where there is more likelihood of injury.

Ledderhose noted obliterative changes in the arterioles of the parameniscal tissues and gave as his opinion that this might be a factor in causing degenerative changes in the cartilage. Kleinberg has stated his belief that the degenerative process is initiated by a local change in cell metabolism or perhaps by injury to blood or lymphatic channels. Burman and Sutro noted that in cartilages taken from joints of persons past the third decade of life there is normally a mucoid degeneration, without cyst formation, however. They said that cyst formation from these areas is possible, though they have not observed it. The majority of cysts occur, as noted in the table, in the age group from 15 to 25 years, so that it seems unlikely that senile changes in the cartilage cause many of the cysts.

Ollerenshaw, Zäch-Christen, Küttner and Venezian have expressed the belief that the cysts are congenital in origin because of the type of endothelial lining present. Most authors have considered that this lining is the result of a secondary change, namely, a sphere of compressed fibrous tissue cells.

Majer has stated that trauma plus a congenital factor is the cause.

King has stated that the cysts arise as a result of the activity of cells secreting a gelatinous fluid. "Certain cells enlarge and secrete mucoid material into the connective tissue between them; some of this material becomes more fluid and cysts form; these gradually enlarge and the cells in the neighborhood revert to their original spindle form. In other words, a joint cavity is formed."

Geschickter and Lewis have said that the fact that the cysts develop at the point of junction of the perichondrium and the synovia at the joint margin suggests that these cysts are synovial inclusions. They have expressed the belief that the cysts are akin to those that arise in the synovial membrane and to ganglions developing in tendon sheaths. They have noted that their origin is in "regressive mucoid changes in pre-cartilaginous tissue."

Zadek and Jaffe expressed the opinion that the cysts may be the result of synovial implants into the cartilage at the time of trauma.

It does not seem improbable that a cyst may arise by any of these various theoretical processes. Careful study of a large number of specimens would probably show that more than one type of cyst does exist.

In our opinion Taylor's theory of a blow over the exposed portion of the cartilage seems to carry considerable weight. From a study of the age group in which these cysts are most common and from the

fact that the lateral cartilage is most exposed and that cysts are not seen with tearing injuries of the cartilages, we feel that we have a real lead as to their origin.

#### TREATMENT

There is unanimity of opinion as to the treatment. Excision of the cyst with the cartilage effects a cure in all instances. Excision of the cyst alone results in recurrence in a high percentage of cases. The fact that the cyst recurs when the cartilage is retained seems to warrant the assumption that the cartilage itself is the source of origin of the cyst.

Methods of removal vary with the technic to which each operator is accustomed. Removal usually requires that the capsule of the joint be opened more widely than for simple removal of a torn meniscus. Hence it is a procedure requiring from four to eight weeks before full return to normal function is attained.

#### PATHOLOGIC FEATURES

The cysts are from 1 to 5 cm. in diameter and protrude from the cartilage along its capsular border in the middle or anterior third. They have a definite limiting membrane which is grayish or yellowish white, depending on the color of the enclosed gelatinous fluid. The consistency of the fluid is that of egg white. On section the cyst is usually multilocular. The larger portions are located outside the cartilage, appearing in the fibrous tissue of the capsule. Only cysts that are 1 or 2 mm. in diameter are located in the meniscus proper. Rarely does the cyst present within the joint, giving symptoms of synovial irritation. Duval and Moutier and Lecène have reported cases in which the cyst arose near the anterior border of the lateral cartilage and was not connected with the meniscus itself. It apparently arose from the region of the patellar ligament.

Microscopically the cysts are filled with a structureless hyaline or mucoid material. The lining of the cavity varies from a thin mesothelial-like wall to a rather thick wall, seemingly composed of compressed fibrous tissue cells. Venezian has described villous projections of the wall, but the evidence does not appear conclusive that these are true synovial-lined cavities.

The ground substance about the cysts is the normal fibrocartilage of the meniscus or the fibrous tissue of the capsule. Occasionally the surrounding structures show a few round cells, as evidence of an irritative process, but no signs of active inflammation have been reported. Meniscitis is a recognized pathologic entity, however. Estor described a case of chronic traumatic meniscitis.

Ledderhose described arteriolar thickening about the cysts, but the majority of specimens have shown no such change. It is more probable that these changes are part of the physiologic ageing of the cartilage, as are the mucoid degenerative changes described by Burman and Sutro.

#### CASE REPORTS

CASE 1.—R. S., a 39 year old physician, was admitted to the hospital on June 19, 1932, because of pain in the left knee.

*History.*—The family history was unimportant.

Three weeks before the patient's admission to the hospital pain and tenderness developed about the lateral aspect of the left knee. The pain radiated down into the foot and up into the thigh. It was an aching pain, at times intense, and sometimes it disturbed his sleep. The knee was most comfortable when held in slight flexion. Infrequently there was no pain. The patient knew of no injury to the knee and had not noted any local heat, redness or increase in the amount of synovial fluid.

Two weeks before admission he noted a mass just above and anterior to the head of the fibula which gradually increased in size. The mass was not tender, except on deep pressure, and did not vary in size.

*Examination.*—The patient was well developed and well nourished. A general physical examination revealed nothing of note, with the exception of a firm mass, 3 by 0.5 cm. in diameter, over the head of the left fibula. It was firm in consistency and seemed attached to the bone. It was not fluctuant and was tender only on heavy pressure. The motion of the knee joint was not impaired. There was no increase in the amount of fluid, and no relaxation of the joint capsule was noted. The mass did not change in size on movement of the joint. The cruciate ligaments were intact.

The diagnosis was cyst of the left lateral meniscus.

*Operation.*—A 6 inch (15 cm.) incision was made over the lateral aspect of the knee. A translucent cyst was presented beneath the subcutaneous fat. On dissection the cyst was found to be connected with the anterior margin of the external cartilage. The cartilage and cyst were excised intact. The joint was closed in layers in the usual manner.

*Postoperative Course.*—Healing was uneventful, and the sutures were removed on the eighth day. Full use of the leg was regained in six weeks.

CASE 2.—C. H., a 20 year old male student, was admitted to the hospital in May 1934, because of pain in the right knee.

*History.*—The family history was unimportant.

The patient had the usual diseases of childhood without complications. He had had no operations or severe injuries.

About one year before admission to the hospital he twisted the right knee and immediately noted pain and swelling in the region of the joint. He was treated in the Walter Reed Hospital, in Washington, D. C., for several days. After the subsidence of the acute symptoms the knee was much better, but an aching pain persisted. He complained of a tired sensation in the knee after walking or athletics. He had not noted any slipping or locking of the joint.

*Physical Examination.*—The patient was well developed and well nourished. The cervical glands were enlarged slightly. There was a soft systolic cardiac murmur. Otherwise, the general physical examination did not show anything remarkable.

The right knee presented a small mass, 2 by 2 cm. in diameter, that was visible and palpable on the lateral aspect of the knee joint. It was apparently attached to the head of the tibia. It was firm and was not tender or fluctuant. There was no local heat or redness. Motion in the joint was not limited; in fact, slight hyperextension was noted. There was no relaxation of the capsular structures, though the anterior cruciate ligament seemed somewhat lax. When the patient stood or the knee was hyperextended, the mass increased slightly in size and became much more tense. There was no increase in the amount of synovial fluid.

The diagnosis was cyst of the lateral meniscus or a bursa beneath the lateral hamstrings.

*Laboratory Examination.*—The Wassermann reaction was negative. The blood and urine were normal.

*Operation* (May 28, 1934).—An incision was made over the mass parallel to the course of the meniscal attachment. A translucent multilocular cyst was immediately encountered beneath the subcutaneous fat, arising from the lateral meniscus

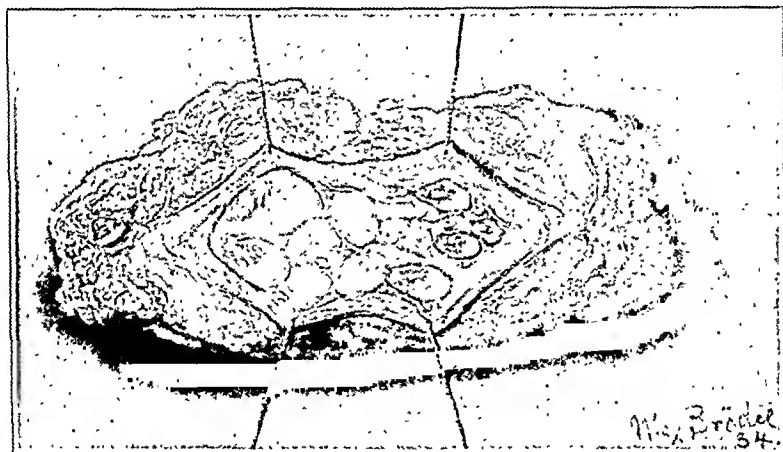


Fig. 2 (case 2).—Gross appearance of the fresh specimen.

by a broad base. The cyst and the cartilage were removed intact. The joint was closed, the capsule being plicated for about 1.5 cm.

*Postoperative Course.*—The wound healed by first intention. Full use of the knee was regained in eight weeks.

*Pathologic Report.*—The specimen consisted of semilunar cartilage, 4 cm. long. Its surface was smooth and appeared normal. With it, however, was included a large amount of flexible, tough, somewhat translucent material of unusual amount and appearance. On section it was seen to merge insensibly with the cartilage. The general appearance was that of a tumor arising from the semilunar cartilage. The cut surface showed several small cystlike areas containing gelatinous material. These apparently communicated with each other and might well have been cysts formed in this tissue. Their appearance was more like that of degeneration tissue, however, than tumor tissue. Two blocks were taken, and sections showed normal fibrocartilage microscopically. In the soft tissue about these areas were a number of collapsed cysts lined with mesothelial cells similar to those present in the cavities of joints. In some places the lining was thickened



by hyaline connective tissue. Elsewhere the stroma was loose. These features were shown to a more advanced degree in the section from the second block. The amount of fibrous tissue suggested the presence of a tumor, but the general appearance was like that seen in case 3, which was more like the appearance of an inclusion cyst resulting from trauma.

The diagnosis was multiple cysts of the semilunar cartilage.

CASE 3.—E. P., a 23 year old male Negro student, was admitted to the hospital on June 9, 1934, because of pain in the right knee.

*History.*—The family history was unimportant.

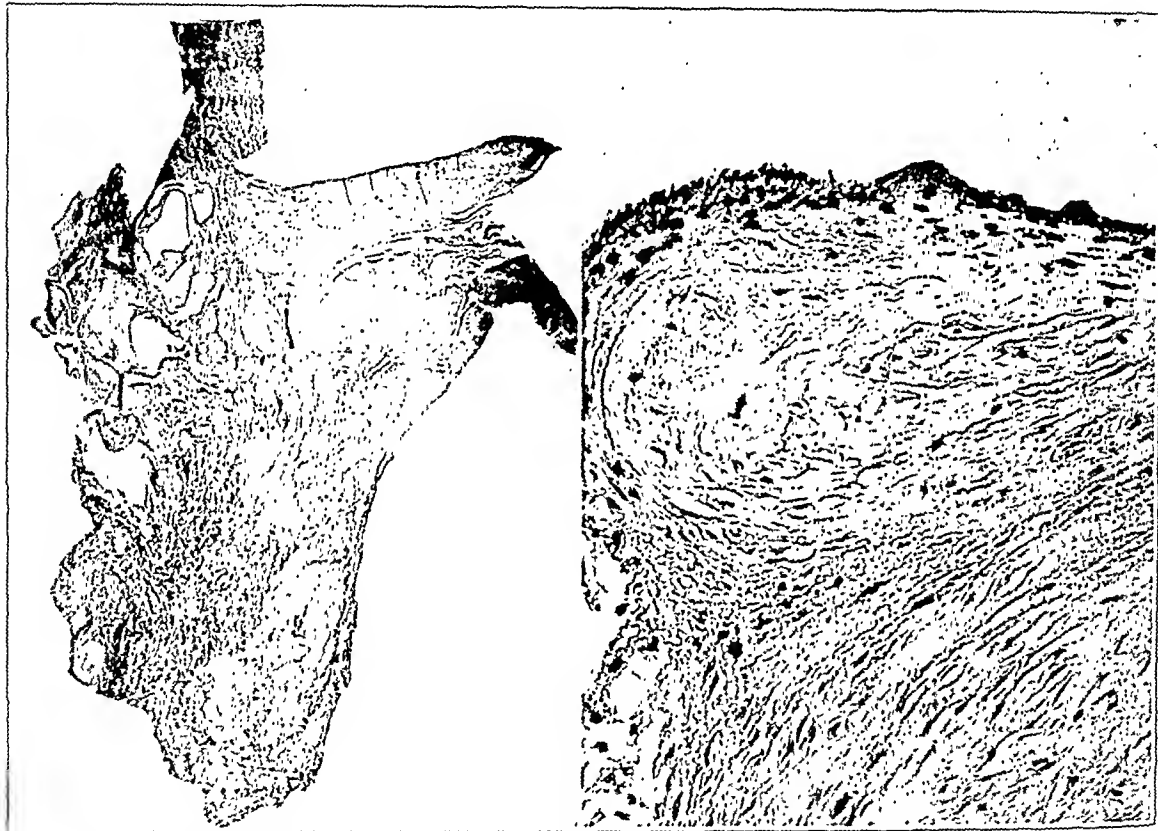


Fig. 3 (case 2).—Low and high power photomicrographs of a cross-section of the cyst.

The patient had measles, mumps, whooping cough and chickenpox as a child and pneumonia in 1917.

In the fall of 1932 the patient was "clipped" while playing football. He had immediate pain followed by swelling of the right knee. The painful area was first on the lateral and then later on the medial aspect of the joint. The knee was swollen for several days, after which the swelling subsided but the pain persisted when the patient walked. The knee was injured again in the fall of 1933 in a similar manner. Since then the patient had noted discomfort and clicking on the medial side of the joint. For two months he had noted some swelling over the painful area. There had been no locking or increase in the amount of synovial fluid since the initial injury.

*Examination.*—A general physical examination showed that the patient was well developed and well nourished. The rest of the examination was essentially normal, except for a soft systolic cardiac murmur heard in the mitral and pulmonic areas and thought to be of functional origin.

There was full range of motion in the right joint. There was tenderness over the anterior attachment of the medial meniscus, and in this region there was a small tumor, measuring 1.5 by 1.5 cm. It was firm and elastic in consistency and seemed attached to the margin of the tibia. There was no increase in the amount of synovial fluid, and no relaxation of the articular capsule or of the cruciate ligaments was noted.

The diagnosis was bursa or cyst of the right medial meniscus.

*Treatment.*—The area was treated with local diathermy, with no improvement as regards either pain or swelling. Exploration was advised.

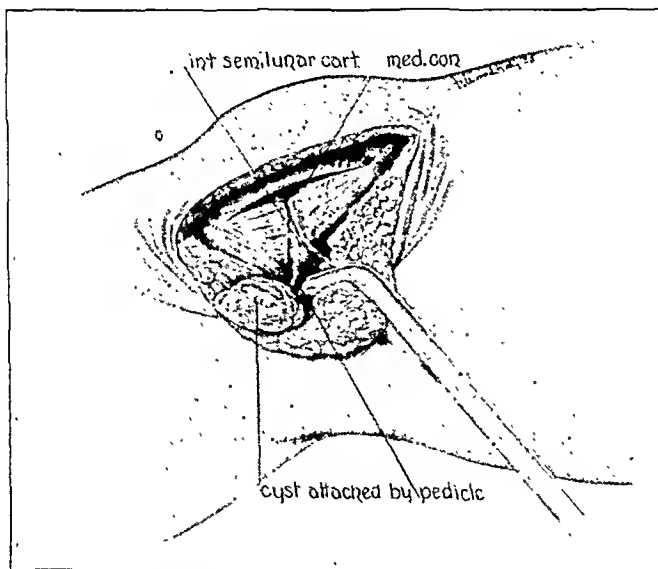


Fig. 4 (case 3).—Drawing of the appearance of the cystic mass at the time of operation, showing the origin from the cartilage by a pedicle.

*Operation* (June 11, 1934).—The right knee joint was entered through the medial parapatellar route. The meniscus was intact. The skin flap was then dissected back over the area where the tumor was presenting. A translucent cystlike mass was at once encountered. When an attempt was made to free it, the cyst wall was ruptured, and a small amount of clear, viscid material escaped. The cyst was freed and was found to be attached to the medial meniscus by a short pedicle. The meniscus and the cyst were removed intact. The joint was closed in the usual manner with some plication of the capsule.

*Postoperative Course.*—There was a severe local reaction in the wound on the seventh day following operation. The temperature was 103 F. The wound was opened. Cultures of material from the wound were sterile. The severe reaction was thought to be due to the catgut used. Healing was associated with considerable stiffness, owing to contracture of the soft tissues. Motion was regained by means of physical therapy and manipulation under anesthesia, followed by myositis ossifi-

cans of the quadriceps femoris and the remnant of cartilage attached to the posterior medial ligament. Full restoration of function was obtained after prolonged physical therapy. The disability lasted for twelve weeks.

*Pathologic Report.*—Dr. Vandegrift reported that the specimen of semilunar cartilage appeared to be normal. With it was included more than the usual amount of fibrous material. The cut surface showed several small translucent areas which looked like cysts and contained soft, gelatinous material. Microscopically, cross-sections of the cartilage appeared to be normal, but attached to the cartilage was a fair amount of soft tissue which presented an unusual feature, in that it con-

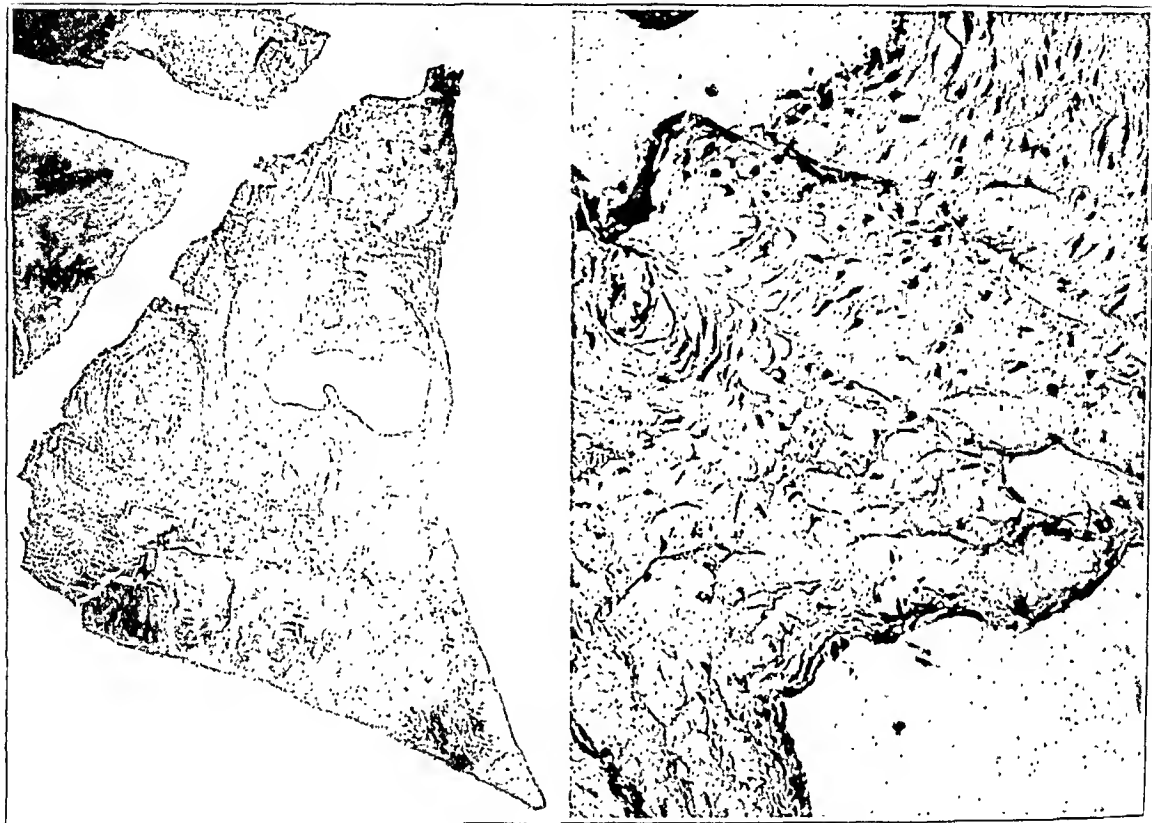


Fig. 5 (case 3).—Low and high power photomicrographs of the specimen.

tained several small cysts lined by flat mesothelial-like cells similar to those found lining the cavities of joints. About the largest cyst were a number of smaller ones. None of these cysts was in the cartilage itself, and all were without content in the section. These cysts had the appearance of mesothelial inclusions and could well have been due to trauma. It was interesting to compare these sections with those in case 2, which showed these changes to a more marked degree.

The diagnosis was multiple cysts of the right medial semilunar cartilage.

*CASE 4.*—L. A. J., a 40 year old meat cutter, was admitted to the Church Home and Infirmary because of painful swelling of the right knee.

*History.*—The family history was unimportant.

The patient had the usual diseases of childhood without complication. He had typhoid at 18. Left inguinal herniorrhaphy was performed in 1931.

About one year previous to admission the patient began to have pain in the right knee. A few months later he noted a small swelling on the medial aspect of the right knee. The pain was aching in character and continued intermittently. The swelling has gradually increased. Extension of the knee aggravated the pain. The patient could not recall any injury to the knee.

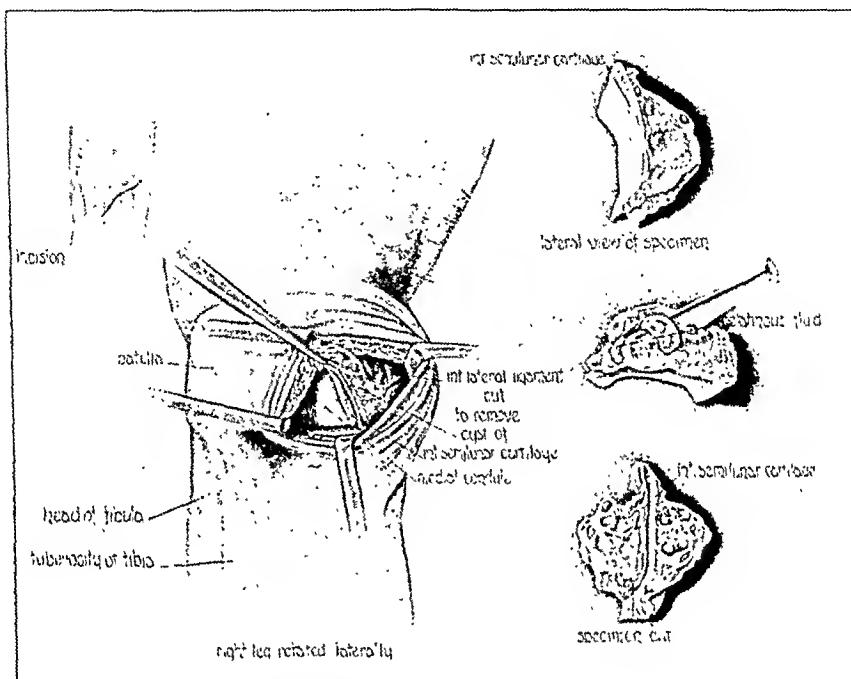


Fig. 6 (case 4).—Drawing showing the location of the cyst, the line of incision, the operative procedure, and the gross appearance of the cyst in toto and in cross-section.

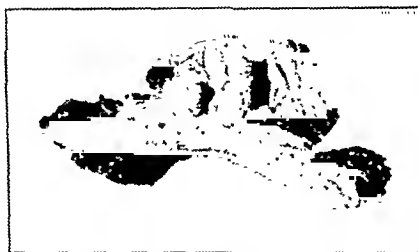


Fig. 7 (case 4).—Photograph of the gross specimen showing the cysts held open with pieces of cork. This is a longitudinal section with part of the cartilage removed.

*Examination.*—The patient was a well developed and well nourished man. The teeth were carious, and the tonsils were enlarged. There was a scar in the left inguinal region; the right inguinal ring was relaxed.

A small swelling was present on the upper end of the tibia on the mesial aspect of the knee. The mass was fluctuant and tender to pressure.

The diagnosis was bursa or cyst of the cartilage of the medial aspect of the right knee.

*Operation.*—The internal semilunar cartilage and a cyst were excised from the right knee on Oct. 16, 1934.

*Postoperative Course.*—The wound healed per primam.

*Pathologic Report.*—Dr. Sprong reported that the specimen of semilunar cartilage had fibrous tissue attached along its outer margin. The entire mass measured 5 by 3 by 1.5 cm. The fibrous tissue along the edge contained a number of cystic areas with a smooth lining. Cross-sections of this fibrous tissue showed

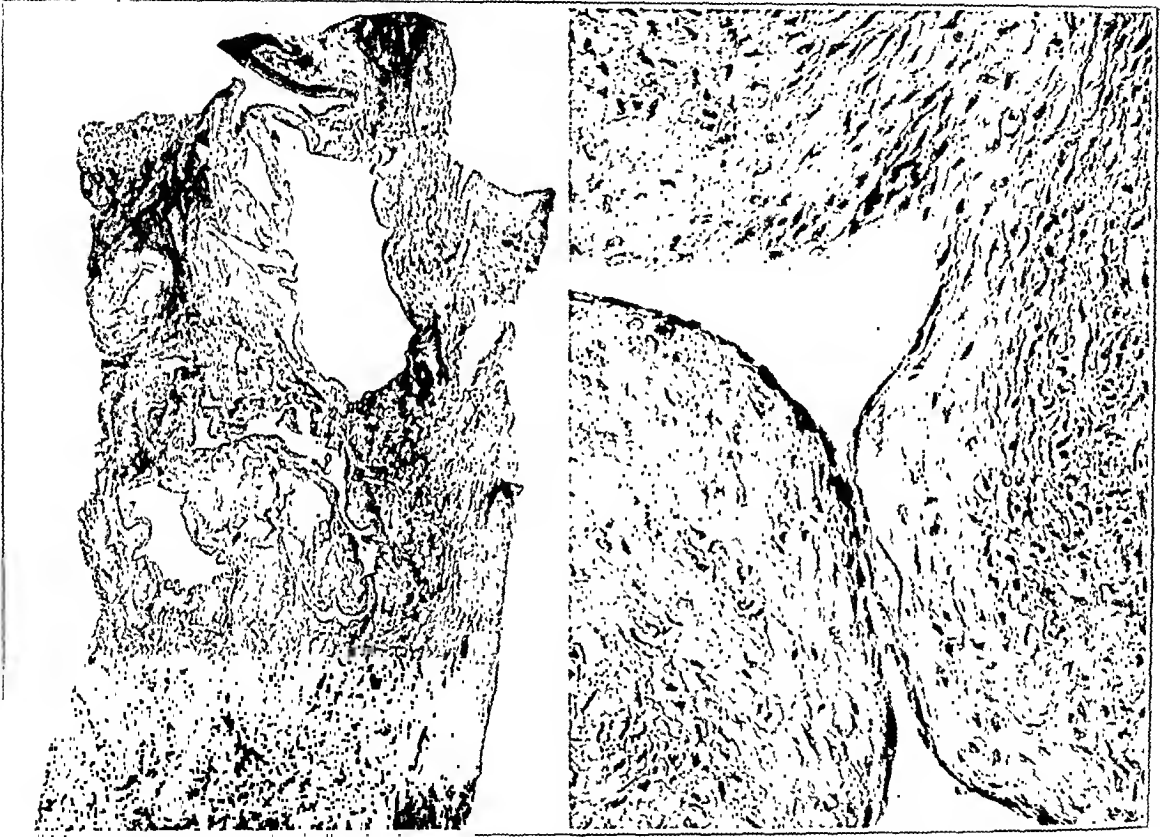


Fig. 8 (case 4).—Low and high power photomicrographs of the specimen.

at one edge normal appearing fibrocartilage and dense fibrous tissue. Attached to this was an area of connective tissue which was much more cellular and throughout which were many irregular spaces lined by a modified connective tissue which appeared like synovial membrane. These varied in size from tiny capillary spaces to large irregular spaces 4 or 5 mm. across. No evidence of neoplasm was seen.

The final diagnosis was multiple cysts of the medial semilunar cartilage of the right knee.

#### SUMMARY

From the 159 cases of cyst of the meniscus of the knee reported in the literature an analysis has been made as to the location, age group, signs, symptoms and pathology of cysts of the semilunar cartilages.

A cure can be obtained by extirpation of the cyst with the meniscus.

This type of cyst probably arises in a traumatized area in the capsular border of the cartilage, which undergoes mucoid degeneration and cyst formation. The cysts are ganglions of the menisci.

Four cases of cyst of the meniscus of the knee are presented.

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# CUTANEOUS HYPERALGESIA OF THE ABDOMEN

## AN EXPERIMENTAL STUDY

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Cutaneous hyperalgesia has achieved a position of some interest in the diagnosis of those acute diseases of the abdomen for which surgical intervention is indicated. However, the mechanistic causation of this somatic manifestation remains somewhat obscure and speculative and therefore appears to be worthy of further experimental study.

Subsequent to the publication of Ross'<sup>1</sup> memorable work on referred pain in visceral diseases, Mackenzie,<sup>2</sup> in 1893, noted areas of cutaneous hyperalgesia in association with such diseases. The increase in sensitivity in these regions was explained by postulation of a viscerosensory reflex, whereby bombardment by afferent splanchnic stimuli from an inflamed viscus produced an irritable focus in the gray matter of the spinal cord, with a resulting increase in the excitability of the sensory nerves of the abdominal wall which enter the affected segment. The observations of Sir Henry Head<sup>3</sup> on the segmental innervation of the skin, in connection with his study of herpes zoster, have been assumed to support this hypothesis.

Morley<sup>4</sup> questioned this orthodox theory of a viscerosensory mechanism of production of associated pain, pointing, among other things, to the unilateral distribution of the alteration in sensation and to the fact that the points of maximum hyperalgesia do not invariably correspond to the segmental innervation of the inflamed viscus presumably involved. He wrote convincingly on the subject and suggested that the presence of a peritoneocutaneous radiation, in which the nerve pathways are somatic only, would be a more logical explanation of the occurrence of the pain.

Lennander's<sup>5</sup> investigations disclosed that the parietal peritoneum and its subserous layer are richly supplied with cerebrospinal sensory nerves. Ramström,<sup>6</sup> in 1908, proposed to test this membrane for

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pressure sense, having already demonstrated the presence of pacinian corpuscles. In his experiments, after the incision was made through the wall of the abdomen, with the area under cocaine anesthesia, the neighboring peritoneum was tested by insertion of a rubber-covered finger and a flat spatula. Lennander demonstrated that there is no pressure sense of the parietal peritoneum. He was convinced, however, that this membrane is endowed with an acute pain sense. The experiments of Capps and Coleman<sup>7</sup> have shown conclusively that pain is elicited by stimulation of the parietal peritoneum and localized (with considerable accuracy) to within 1 inch (2.5 cm.) of the point irritated. The positive response to the Blumberg "rebound" test which occurs in cases of acute appendicitis, cholecystitis, etc., has been explained by the suggestion that the sudden release of pressure causes a suction between the visceral and the parietal layer of the peritoneum, the resulting irritation of the parietal layer, with its contained cerebrospinal receptor endings, producing pain.

My purpose in this investigation was to determine the effect, if any, of irritation of the parietal peritoneum on production of cutaneous hyperalgesia. From the nature of the study it is obvious that observations on animals would be unsatisfactory. Therefore, experimental methods were applied to human subjects at the Methodist Hospital of Indianapolis during the course of operative procedures for various abdominal lesions.

#### METHOD OF STUDY

The subjects were chosen at random, irrespective of the degree of sensitivity of the patient to external stimuli. The preoperative medication consisted of oral administration of 9 grains (0.6 Gm.) of sodium amytal during the twelve hours preceding operation, with  $\frac{1}{6}$  grain (0.01 Gm.) of morphine sulfate administered hypodermically just prior to operation. After incision of the abdominal wall (which had been anesthetized by local infiltration with a 0.5 per cent solution of procaine hydrochloride without epinephrine) the experiments were carried out essentially according to the method of Ramström. However, in order to facilitate and maintain adequate exposure of remote areas of the parietal peritoneum selected for testing, it was found to be necessary to improvise certain instruments. A slightly curved tube, 2 cm. in diameter and 18 cm. in length, with a fenestration of 1.5 cm. throughout its anterior length, was fashioned of sheet metal, and to it was welded a flat handle 10.5 cm. in length. The polished inner surface of the tube favored transmission of reflected light (fig. 1). A second instrument consisted of a slightly curved uterine sound, to the tip of which was brazed an elliptic metal terminal, so machined that the flat surface, which measured 1.3 by 2.5 cm., possessed numerous, relatively sharp studs (fig. 1). A standard olivary-tipped uterine sound and a French dressing forceps were also used. Through the various operative wounds, the metal tube (which might be termed an abdominoscope) was introduced into the abdominal cavity in a position contiguous to the surface of the

7. Capps, J. A., and Coleman, G. H.: Localization of Pain Sense in Parietal and Diaphragmatic Peritoneum, *Arch. Int. Med.* 30:778 (Dec.) 1922.

parietal peritoneum (fig. 2). Through the tube anterior and lateral areas of this membrane, from the periphery of the diaphragm to the pelvic inlet (7.5 to 15 cm. remote from the outermost border of the anesthetized zones), were irritated

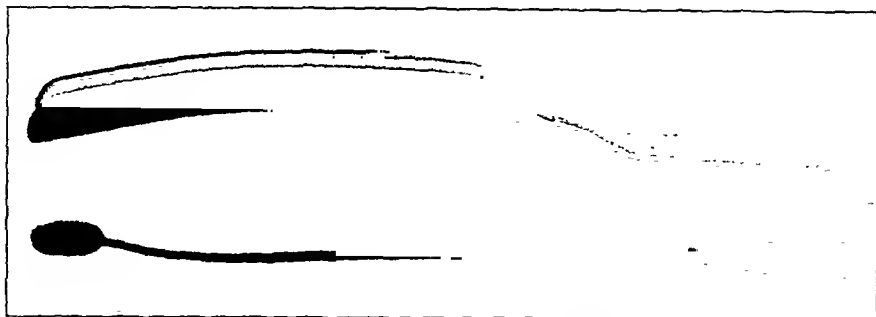


Fig. 1.—Improvised instruments.

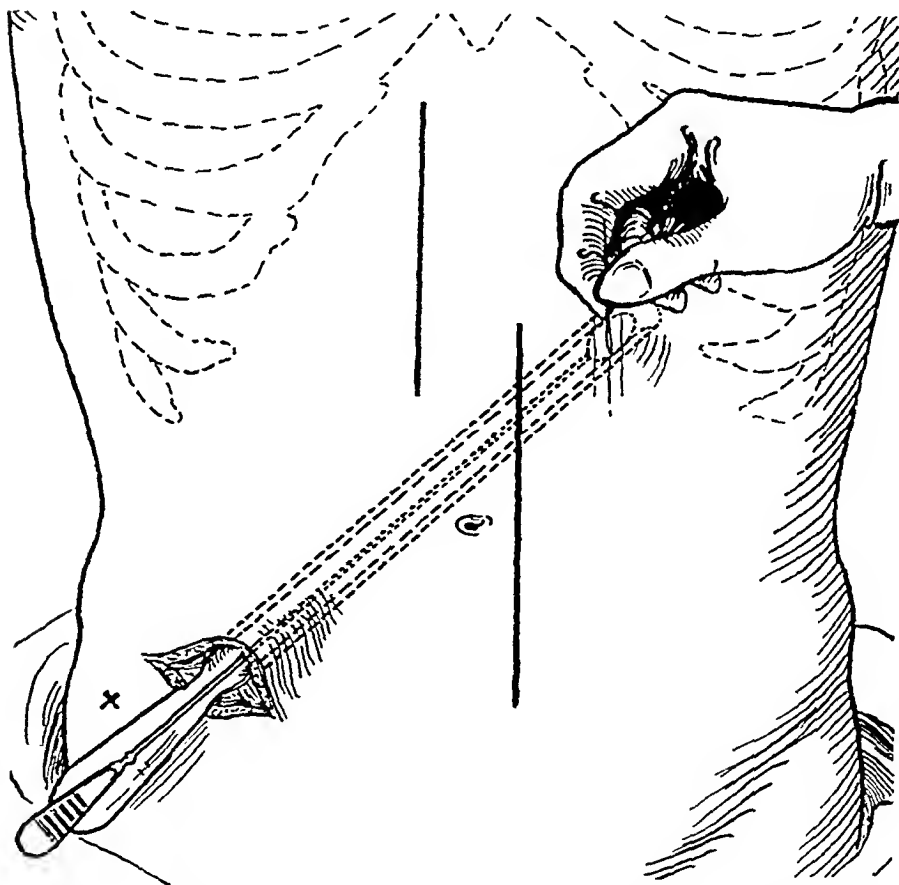


Fig. 2.—Method of eliciting cutaneous hyperalgesia through a modified McBurney incision. This was repeated through the other incisions indicated by the heavy black lines.

by various stimuli. The skin overlying these and adjacent areas was then tested for cutaneous hyperalgesia by light stroking with the blunt end of a large cambric needle (fig. 2).

## RESULTS

It will be noted in the accompanying table that irritation of the parietal peritoneum by contact with a blunt instrument or a sponge moistened with a saline solution produced no increase in the sensitivity of the skin. In five cases the phenomenon of referred pain was present in a mild degree after stimulation of the parietal peritoneum by

*Results of Experiments*

Case	Diagnosis	Incision	Regions Irritated	Hyperalgesia Produced with Various Stimuli					
				Sponge Wet with Saline Solution		Standard Olivary-Tipped Sound		Sharp-Studded Instrument	
				Con-tact	Move-ment	Con-tact	Move-ment	Con-tact	Move-ment
1	Chronic appendicitis	McBurney	Inferior border of upper zones	—	—	—	—	+	+
			Left lumbar region	—	— +	—	—	+	++
			Left iliac region	—	+	—	—	+	++
2	Chronic cholecystitis	Vertebral upper right midrectus	Left hypochondriac region	—	—	—	—	— +	— +
			Left lumbar region	—	— +	—	—	+	+
			Lower zones	—	—	—	—	+	+
3	Chronic appendicitis	McBurney	Inferior border of upper zones	—	—	—	—	— +	— +
			Left lumbar region	—	—	—	—	+	+
			Left iliac region	—	—	—	—	+	+
4	Chronic appendicitis	McBurney	Inferior border of upper zones	—	—	—	—	— +	+
5	Chronic appendicitis	McBurney	Inferior border of upper zones	—	— +	—	—	+	+
			Left lumbar region	—	+	—	—	++	++
			Left iliac region	—	+	—	—	++	++
6	Early acute endo-appendicitis	McBurney	Inferior border of upper zones	—	—	—	—	— +	— +
			Left lumbar region	—	— +	—	—	+	+
			Left iliac region	—	— +	—	—	+	+
7	Chronic appendicitis	McBurney	Inferior border of upper zones	—	—	—	—	—	— +
			Left lumbar region	—	—	—	—	—	— +
			Left iliac region	—	—	—	—	+	+
8	Recurrent appendicitis	McBurney	Inferior border of upper zones	—	—	—	—	—	— +
			Left lumbar region	—	— +	—	—	+	+
			Left iliac region	—	— +	—	—	+	+
9	Carcinoma of cecum	Left rectus midpoint at umbilicus	Right hypochondriac region	—	—	—	—	—	—
			Right lumbar region	—	—	—	—	— +	— +
			Right iliac region	—	—	—	—	— +	+

application of the moistened sponge with a vibratory motion. Irritation by an instrument with sharp points produced cutaneous hyperalgesia: a response which, though varying in degree, manifested itself in all the cases. There was no appreciable difference in the degree of dysesthesia experienced on opposite sides of corresponding regions of the abdomen. However, a slightly greater increase in cutaneous hyperalgesia occurred in areas situated below the transverse plane of the umbilicus than in areas located above this plane. Incidentally, although data relative to

this observation are not included in the table, the points of maximum hyperalgesia were found to be immediately overlying the area irritated. This corroborates the observations of Capps and Coleman as to the localizing power of the parietal peritoneum. However, owing to the nature of the experiment, no attempt was made to determine the exact extent of the radiation or duration of the aberration of sensation. In the nine experiments tabulated the patient was conscious of localized discomfort at the point irritated, but every effort was made to avoid the production of definite spontaneous pain, so that such pain might not be confused in the mind of the subject with cutaneous hyperalgesia. However, as a matter of experimental interest, it was noted that pressure on the parietal peritoneum sufficient to produce an appreciable prominence in the overlying abdominal wall elicited pain in each instance, thus further confirming the observations of other investigators as to the sensitivity of this membrane.

It is fully realized that because of the variability of response to all tests for sensation and the difficulties necessarily encountered in this type of investigation, conclusions must be drawn with reservations. However, it is felt that the results obtained are sufficient to permit the making of deductions, which are more than impressionistic.

#### CONCLUSIONS

1. The findings described appear to confirm the results of the experiments of Lennander, Ramström, Capps and Coleman, and Morley as to the acute pain sense possessed by the parietal peritoneum in the regions explored, i. e., the anterior and lateral areas from the periphery of the diaphragm to the pelvic inlet.

2. The point of maximum cutaneous hyperalgesia elicited by adequate irritation of the parietal peritoneum, like spontaneous pain, is localized in the area of the abdominal wall immediately overlying the area of stimulation.

3. Cutaneous hyperalgesia may be produced by irritation of the parietal peritoneum. In cases of such artificial stimulation, since no visceral nerves are involved, the productive mechanism appears to be a peritoneocutaneous radiation.

# DIFFUSE GENUINE PHLEBECTASIA

## REPORT OF A CASE

ERNST FREUND, M.D.

VENICE, FLA.

Bockenheimer,<sup>1</sup> in 1907, reported a case in which there was marked diffuse enlargement of the veins of the varicose and cavernous type extending from the palm of the hand into the axillary veins. The arteries were not involved, and there was no arteriovenous communication. He considered the condition as *sui generis* and introduced the term "genuine diffuse phlebectasia," separating this type of venectasia from other forms, such as venous hemangioma (*cirsoideum*) and varicose veins.

I recently had occasion to study a case in which there was enlargement of veins in the shoulder region which showed many of the characteristics of Bockenheimer's genuine phlebectasia. Dr. Steindler, from whose private files the record is taken, gave his permission to report the case here.

## REPORT OF CASE

An 8 year old girl entered the clinic complaining of pain and swelling in the region of the right shoulder. At the age of 4 years a slight swelling of the right shoulder was noted by the mother. The child was seen by a physician, but no diagnosis was made. Since then the swelling had continued intermittently, gradually increasing. It was entirely painless until a few months before the patient's admission to the clinic, when the shoulder ached occasionally. The pain awakened the child sometimes. She was examined in a renowned clinic, where complete laboratory work was done. Examination gave negative results; no diagnosis was made, but exploratory operation was advised.

On physical examination, nothing abnormal could be observed from the front. From the back, a swelling was visible over the right shoulder blade and the posterior portion of the deltoid muscle. The skin was of normal appearance, and there was no increase in cutaneous temperature (on palpation). There was fluctuation over the posterior portion of the deltoid muscle. Within the fluctuant area distinctly small hard nodules the size of a pea could be palpated. Similar nodules were also present over the shoulder blade and in the subscapularis muscle. These nodules were tender. The axilla was free; full motion was possible in the shoulder. The radial pulse was easily palpable; no other changes were noted in the extremity.

The roentgenogram showed some swelling of the soft tissue of the right shoulder region, without changes of the bones but with a few calcified areas within

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1. Bockenheimer, quoted by Schmidt.<sup>8</sup>

the soft tissue. The areas of calcification were, as a rule, well outlined and round, the larger bodies having some concentric structure.

No definite diagnosis was made. A parasitic involvement of the musculature of the shoulder was considered, but because of a lack of general symptoms and because of the varying size of the calcified areas this was dropped as a diagnosis. To arrive at greater clearness, an exploratory operation (Dr. Steindler) was indicated. An aspiration needle was inserted over the fluctuant area, and frank dark blood was obtained. The clinical diagnosis of hemangioma was made, and the patient was given roentgen treatment. Two months later it seemed that the tumor was smaller. The changes shown in the roentgenograms were essentially the same as those noted earlier.

#### COMMENT

This was a case of fluctuant swelling in the shoulder region due to enlargement of venous blood spaces with calcified phleboliths. The lesion started early in childhood and was slowly progressive. Nothing suggested participation of the arteries in the pathologic process. The skin over the region of the shoulder was free from discoloration and appeared normal. The condition, therefore, involved mainly the deeper veins within and under the shoulder muscles. The changes were relatively mild, probably because of the youth of the patient. Further progress of the lesion is to be expected if roentgen treatment is unable to stop its development.

There may be some doubt as to the diagnosis. The clinical diagnosis of venous hemangioma was made. Arterial involvement and traumatic lesion of the blood vessels could easily be ruled out. The relatively moderate extension of the lesion made it difficult to draw a sharp line between venous hemangioma and diffuse phlebectasia. I believe, however, that venous hemangioma, especially if it develops some time after birth, represents probably only a minor degree of diffuse phlebectasia. The diagnosis venous hemangioma or diffuse phlebectasia may in great part depend on the time of observation. If the lesion is observed early, at a time when it is not yet extensive, the diagnosis may be hemangioma; if it is observed late, when a great part or the entire extremity is involved, diffuse phlebectasia will be considered if one is acquainted with the latter picture at all.

#### REVIEW OF THE LITERATURE

A relatively small number of cases have been reported in the literature, which shows either that the condition is rare or that it is not sufficiently known. The fact, however, that only two observers could report two cases and all the others only one is sufficient proof of the rareness of the condition.

Although it is undoubtedly Bockenheimer's merit to have called special attention to the diffuse genuine phlebectasia, it seems that the

clinical picture had been known before. Von Pitha<sup>2</sup> (to quote Sonntag) as early as 1869 so described the venous (cavernous) angiectasia. Von Pitha stated that the lesion starts in the fingers, usually of only one hand, and gradually involves the entire extremity up to the shoulder. It leads to atrophy of muscles and bones. He mentioned phleboliths also as common occurrence. Palmgren<sup>3</sup> (1889), in a dissertation on phlebectasia of the upper extremity, mentioned two cases in which the condition probably belonged to the group of genuine diffuse phlebectasia.

CASE 1.—The patient was a 14 year old girl with congenital venectasia of the index finger, with gradual involvement of the entire dorsal side of the fingers, wrist and forearm. In some places calcified phleboliths were palpable. Extirpation of the enlarged veins was attempted. No follow-up notes were available.

CASE 2.—A 26 year old woman had had venectasia of the left arm since childhood. No pulsation was present. There were numerous calcified phleboliths.

Another case which most likely is an instance of genuine diffuse phlebectasia in the sense of Bockenheimer was reported by Heide<sup>4</sup> in 1906 as one of cavernous angioma of the lower extremity (elephantiasis telangiectodes).

CASE 3.—The patient was a 12 year old boy with a thickened left lower extremity. There were many prominent portions of dark blue or reddish-blue stain; in some places the tumors were raspberry-like and the skin was atrophic. The tumors were easily compressible and disappeared if the extremity was elevated. The muscles and bones were very atrophic. Many phleboliths could be palpated. No pulsation or bruit was present. Besides the extensive changes on the left lower extremity (from the toes to the inguinal region), some telangiectasia could be noted below the clavicle and on the upper part of the arm.

CASE 4 (Bockenheimer,<sup>1</sup> 1907).—The patient was a 52 year old barrel-organ player, in whom at the age of 50, but probably since the age of 20, an enlargement of the veins of the left palm was noted, which gradually continued to the shoulder. The arm grew to twice its normal size and increased 3 cm. in length. Motion in the large joints was well preserved, but motion of the fingers was limited, and there were paresthesia, cramps and pain, incapacitating the patient. The entire arm showed numerous enlarged veins which in part were shining through the atrophic skin. The vena cephalica was especially involved. There was ascending venous pulsation, with a bruit at the wrist. Amputation was performed. There was much venous bleeding from the soft tissues which complicated the postoperative course. The wound became infected, and the patient died. Anatomically, the amputated arm showed enlargement of all the veins into the smallest ramifications.

CASE 5 (Bircher,<sup>5</sup> 1912).—The patient was a 21 year old man. When he was 4 weeks old, his mother noted at the right elbow a small blue spot, gradually

2. von Pitha, quoted by Sonntag.<sup>6</sup>

3. Palmgren, quoted by Sonntag.<sup>6</sup>

4. Heide, H.: Ein Fall von linksseitigem cavernösem Angiom der Unterextremität, regg. glutaea, perinealis et pudendalis (Elephantiasis telangiectodes), Arch. f. klin. Chir. 80:827, 1906.

5. Bircher, E.: Genuine Phlebektasie des Armes, Arch. f. klin. Chir. 97:1035, 1912.



increasing in size. The arm became enlarged, and there was occasional pain at night. The arm was markedly thickened, especially on the ulnar side, where a great number of soft and compressible tumors were present, belonging to the superficial and deep veins. There was no discoloration of the skin and no communication between the veins and arteries. A radical excision of the widened veins was performed. They were in great part adherent to the skin. The musculature was involved and was atrophic around the veins. Numerous phleboliths of different sizes (the largest like hazelnuts) were encountered. After the operation the venectasia recurred quickly, but the patient felt improved.

CASE 6 (Sonntag,<sup>6</sup> 1918).—A 17 year old boy had had "varicose veins" on the left lower extremity since the age of 14. On physical examination a hemangioma of the size of an egg was noted on the left thigh, with several smaller ones in the neighborhood. Diffuse phlebectasia was present from the foot to the groin in the form of thick, dark blue, soft, compressible convolutes. The



Fig. 1.—Diffuse phlebectasia in the right shoulder region in an 8 year old girl. Several calcified phleboliths are shown in the shoulder muscles.

distribution did not correspond to that of varicosities of the saphenous vein. Within the enlarged veins small movable hard bodies could be palpated, slightly tender to touch—phleboliths. They did not show in the roentgenograms. The leg was 1 inch (2.5 cm.) longer than the other.

CASE 7 (Drissler,<sup>7</sup> 1921).—The patient was a 15 year old boy. Since birth a blue area had been present over the left lower quadrant of the abdomen, with blue strips on the left lower extremity, caused by diffuse phlebectasia. In the popliteal fossa hard nodules the size of peas were palpable. No pulsation was present. No difference could be noted in the cutaneous temperature between the affected and the normal extremity. No atrophy of the muscles was present; the involved limb was shortened 2 cm.

6. Sonntag: Ueber genuine diffuse Phlebektasie am Bein, München' med. Wchnschr. 66:155, 1919.

7. Drissler, Emmy, quoted by Sonntag.<sup>6</sup>

CASE 8 (Schmidt,<sup>8</sup> 1926).—A 17 year old boy had "varicose veins" of the right arm and hand. Immediately after birth fine veins could be noted on the right wrist and forearm. During the first year of life the veins enlarged, and an irregular nodular tumor developed on the hand and forearm. The enlargement of the veins soon extended to the upper part of the arm, the chest and the back. The right arm was always larger than the left. There was no particular complaint

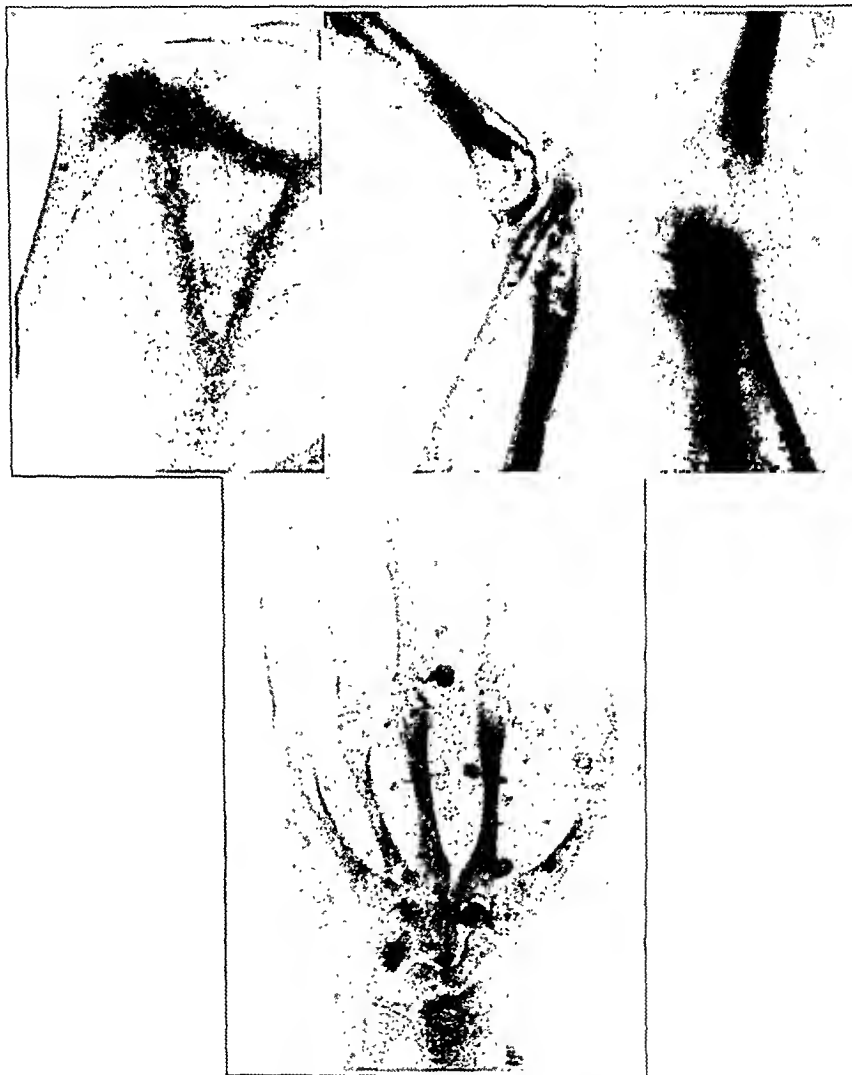


Fig. 2.—Illustration taken from Schmidt's article (*Deutsche Ztschr. f. Chir.* **198**:403, 1926). The patient was a 17 year old boy with numerous phlebotitis in the ectatic veins of the right upper extremity.

except of some sensation of heaviness and fatigue. The grip of the right hand was always weak; the elbow could not be fully extended, and the patient had

8. Schmidt, A.: Genuine diffuse Phlebektasie am Arm, *Deutsche Ztschr. f. Chir.* **198**:403, 1926.

little use of this extremity. On physical examination diffuse venectasia of the right upper extremity was observed, extending from the fingers to the chest and back. The widened veins formed dense convolutes, or slings, some of which were thick like a thumb. They formed a cavernous tissue, which could easily be compressed with the hand. The swelling of the extremity was reduced when the arm was lifted up. In the deeper tissues, holes could be palpated, through which the widened veins passed. In many places hard nodules were present, slightly movable, which gave a characteristic roentgen shadow of phleboliths. The smallest were the size of a pinhead, the largest the size of hazelnuts. Some of the larger phleboliths showed one or two dark centers with irregular outlines. Others were built concentrically. The arm was 2 cm. longer than the other. The bones were gracile and thin and looked like those of a 10 year old girl.

CASE 9 (Orel,<sup>9</sup> 1926).—The patient was a 6 year old boy. A short time after birth, in different portions of the left lower extremity, numerous enlarged veins of varying size were noted. In some places they were so dense that they appeared as dark blue strands through the skin. No pulsation could be felt, and the vessels were easily compressible. Some thrombi and phleboliths were palpable. The venectasia extended from the dorsum of the foot along the outer side of the leg to the posterior aspect of the thigh. The veins of the penis were also ectatic.

CASE 10 (Susman and McCredie,<sup>10</sup> 1927).—This was the first observation reported in the English literature. The patient was a 15 year old girl with gradually increasing painless swelling of the right arm. The only complaint was of some numbness after long maintenance of a pendent position of the arm. The upper part of the arm was 2 inches (5 cm.) thicker than the left arm; the forearm was 1 inch (2.5 cm.) thicker. No edema was present. The upper third of the upper part of the arm and the anterior portion of the wall of the chest on the right showed many markedly enlarged veins. There was no difference in length between the extremities.

CASE 11 (Reichel,<sup>11</sup> 1928).—The patient was a 14 year old girl. Since early childhood extensive venectasia of the entire left lower extremity had been present. There had been gradual increase of the lesion, with severe flexion contracture of the knee joint and equinovarus of the foot. The widening of the veins was especially marked in the region of the saphena magna, with formation of large lobulated tumors on the lateral surface of the thigh. In two places the tumors broke through the skin; they penetrated the musculature and at the time of operation they were observed to be densely connected with the sciatic nerve. The arteries were not involved.

CASE 12 (Sonntag,<sup>12</sup> 1928).—The patient was a 22 year old teacher. Since the age of 4 years there had been gradual enlargement of the right forearm, starting at the radial side of the wrist joint and progressing toward the fingers. During the year before examination the condition became worse, with pain, a sensation

9. Orel, H.: Beitrag zur Kasuistik der genuinen diffusen Phlebektasie, *Ztschr. f. Kinderh.* **42**:668, 1926.

10. Susman, Eric, and McCredie, D. W.: Hemangiectatic Hypertrophy of the Arm: A Case of Genuine Phlebektasia, *M. J. Australia* **2**:581, 1927.

11. Reichel, P.: Report on the Thirteenth Meeting of the Vereinigung miteldeutscher Chirurgen, *Zentralbl. f. Chir.* **5**:2934, 1928.

12. Sonntag: Ueber einen Fall von genuiner diffuser Phlebektasie am Unterarm und Hand, *Arch. f. klin. Chir.* **153**:802, 1928.

of fulness and fever in the arm. On physical examination enlargement of the veins was noted from the elbow downward, especially on the volar side. In a pendent position the forearm was swollen; the swelling disappeared promptly when the arm was elevated. In the deeper layer numerous hard nodules the size of peas could be palpated. No pulsation or bruit was present. There was a 2 cm. shortening of the affected limb and atrophy of the muscles. A roentgenogram showed many calcified phleboliths. The patient was operated on; there was marked venous bleeding. The ectatic veins were ligated and partly excised. Six months after the operation the condition was improved, but a number of venous tumors were present. A second operation was planned.

CASE 13 (K. Akaiwa,<sup>13</sup> 1929).—The original report in Japanese was not obtainable. The patient had diffuse phlebectasia of the left arm.

CASE 14 (Kislicenko and Milisič,<sup>14</sup> 1931).—The patient was a 19 year old youth. At the age of 11 he had cellulitis of the arm. A few months later elevated dark blue spots appeared in the skin of the distal part of the left forearm. There was a gradual and constant increase in the number and size of these areas, with loss of strength and severe pain in the arm. At the time of examination a marked diffuse ectasia of the superficial and deep veins of the left forearm was noted, especially on the ulnar side. A prestage of ulceration was present in the skin of the palm, owing to passive hyperemia. There was atrophy of muscles and bones. No arterial involvement was present, and no bruit was heard.

Another case was reported by Musger, but there is some doubt whether the condition was genuine diffuse phlebectasia.

CASE 15 (Musger,<sup>15</sup> 1932).—The patient was a 24 year old woman. Five years before admission to the hospital she noted a large brown area on the right leg. She made no special complaints. On physical examination a hemangioma was observed on the back. The right calf showed atrophy of the skin, with diffuse enlargement of the veins. Tough strands of thrombosed veins and hard nodules of calcified and even ossified thrombi could be palpated. The roentgenogram revealed numerous calcified phleboliths. On histologic examination the wall of the ectatic veins was shown to be thinned; in some places it was made up only of connective tissue, and in others it was poor in elastic fibers.

#### COMMENT

From the case reported here and the observations collected from the literature, I shall try to give a full description of the clinical picture of genuine diffuse phlebectasia.

It is a slowly progressive lesion of a smaller or larger region of the venous system of an extremity. The upper extremity (nine instances) seems to be more frequently affected than the lower (six instances).

13. Akaiwa, K.: Diffuse Phlebectasia of Left Arm, *Okayama-Igakkaï-Zasshi* 41:1780, 1929.

14. Kislicenko, L., and Milisič, S.: Phlebectasia Diffusa Genuina, *Srpski arh. za celok. lek.* 32:180, 1926; abstr., *Zentralorg. f. d. ges. Chir.* 52:472, 1931.

15. Musger, A.: Ueber einen ungewöhnlichen Fall von Knochenbildung in der Haut zugleich ein Beitrag zur Kenntnis der sog. diffusen Phlebectasia. *Arch. f. Dermat. u. Syph.* 166:201, 1932.

and there have been more men (nine) than women (six) among the patients. The involved area shows enlargement of all the veins, into the finest ramifications, without preference for any special anatomic distribution. There does not seem to be a new formation of vessels, as is the case in true hemangioma. But to separate sharply diffuse phlebectasia from hemangioma even by anatomic investigation is difficult. The difference is probably only one of degree.

The enlarged veins form large strands and tumor-like prominences, over which the skin frequently becomes atrophic, so that the ectatic veins show through the skin as dark blue or bluish red. They can easily be compressed, and they disappear when the extremity is elevated for a while.

The lesion develops spontaneously; it is probably on a congenital basis of a faulty anlage of more or less extensive regions of the venous vessel system. The unilaterality of the involvement, the relatively frequent association with cutaneous hemangioma and the onset usually in early childhood point toward a congenital lesion. Disturbance of vasomotoric innervation has been considered from the etiologic point of view, but there is nothing to substantiate such a supposition.

Anatomic and histologic observations are compatible with congenital maldevelopment of the venous vessel wall. There seems to be a constitutional weakness of the vessel wall. The media is very poor in muscle cells and elastic fibers; the wall consists mainly of collagenous fibers. The intima may show circumscribed proliferative changes without inflammatory signs. Thrombosis, probably due to the anomalous blood flow in the ectatic spaces, is a constant occurrence. Organization with recanalization of the thromboses or calcification and even ossification (Musger) takes place frequently; the presence of numerous phleboliths is of importance in special differential diagnosis.

The symptoms are characteristic, and once one is acquainted with the clinical picture, it is very easy to make the diagnosis. It varies a little, depending on the degree of involvement and whether superficial or deep veins participate. In the latter case, the musculature which is penetrated by the venectasia becomes atrophic, and large defects can be palpated after the blood has been pushed out from the venous sinuses.

The involvement of the extremity may be associated with disturbance of growth in length, either in the sense of lengthening (three cases) or shortening (two cases). The difference cannot simply be attributed to the passive hyperemia. This would explain the increase in length but not the shortening. It may be that the shortening is, like the frequently observed atrophy of the bone, a result of disuse in the sense of a hypoplasia (if one does not think of a more extensive disturbance of growth of the extremity, associated with but not simply caused by

the vascular changes). It is of interest that in Bockenheimer's case lengthening of the extremity was present, although the patient dated his trouble from the age of 50. It is clear that the condition must have started sooner, even before the physiologic growth of the bone stopped.

The lesion is relatively benign and extends over many years. Owing to the atrophy of the muscles and to limitation of motion of the joint (due to the venous swelling), the patients have decreasing use of the affected extremity. Pain and cramps may be present but are not outstanding symptoms. Numbness, paresthesia and ulceration of the skin, with infection and even gangrene, have been observed.

The differential diagnosis has to rule out genuine diffuse phlebarteriectasia, a rare condition with participation of the arteries. (Some authors have expressed the belief that there is no sharp line between diffuse phlebectasia and phlebarteriectasia.) If the lower extremity is involved, varicose veins have to be considered; the beginning in early childhood, the unilaterality of the condition, the frequent coincidence with congenital hemangioma, the lack of strict anatomic distribution and the common occurrence of phleboliths in diffuse phlebectasia will rule out varicose veins. As already mentioned, it is difficult, if not impossible, to differentiate diffuse genuine phlebectasia sharply from hemangioma venosum.

The prognosis is not good. The lesion is progressive and if left alone will sooner or later lead to serious complications (bleeding, ulceration, infection, gangrene, pain, incapacitated function).

*Treatment.*—In four cases reported in the literature the condition was treated surgically. Radical excision and ligation of the enlarged veins were performed with questionable results. Recurrence seems to be the rule. In one instance (Bockenheimer) amputation was performed with fatal outcome, due to uncontrollable venous hemorrhage and infection. In our case roentgen treatment was tried. The swelling of the shoulder was reduced, but the period of observation was too short to warrant any judgment of this form of treatment. It may, however, be indicated in cases in which the involvement is less extensive.

## ETIOLOGY OF DEEP ACETABULUM AND INTRAPELVIC PROTRUSION

A. M. RECHTMAN, M.D.

PHILADELPHIA

The term "intrapelvic protrusion of the acetabulum" was translated by Daub<sup>1</sup> from the German *Intrapelvine Pfannenvorwölbung* and pertains to a lesion of the hip joint. This title partially describes the pathologic process, suggests the picture seen on the roentgen films and is understandable. Many articles under various titles have been written, especially in the German literature, regarding the condition and its etiology. The prime purpose of this paper is to discuss the development of the acetabulum and its relationship to the etiology of the deep acetabulum and of intrapelvic protrusion.

The complaints of most patients suggest arthritis of one or both hips, frequently with no involvement of other joints. Pain and stiffness on change of position, with limited motion of the joint, are usual. The discomfort is aggravated by motion, and the patients often walk with an awkward gait or limp. Although the discomfort may be referred to one hip, the examination may show that both are involved. It is noteworthy that in each of the five cases to be reported the same motions were restricted on both sides.

On physical examination of a patient with a congenitally deep acetabulum, the extremity is usually found to be in an attitude of abduction and external rotation. After intrapelvic protrusion occurs, this attitude persists and flexion and extension are often free. Restriction of motion occurs because of the deep position of the head of the femur in the acetabulum, with the approximation of the trochanters to the side of the pelvis. The trochanters are but slightly elevated, and the limb is somewhat shortened. The clinical picture changes, depending on the cause for the intrapelvic protrusion and later on the severity of the condition or infection localized and causing irritation in the hip joint.

On roentgen examination of a patient with the clinical picture as outlined, a deep acetabulum or one with a protrusion of the inner wall into the pelvis may be shown. In the former the cavity is deeper and larger, and its inner wall is thinner than normal. In intrapelvic pro-

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From the Jewish Hospital, Philadelphia.

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1. Daub, H. P.: Intrapelvic Protrusion of the Acetabulum, *Radiology* **12**: 369, 1929.

trusion the head of the femur usually appears elongated because of vegetative growths on the margins of the head and of the acetabulum, which overhang the neck of the femur. The head of the femur is intact, assumes the shape of the acetabulum and is displaced into the deepened, enlarged and often dome-shaped cavity. The inner wall of the acetabulum protrudes to various degrees into the pelvis. It may be paper thin and is usually sclerotic. The joint space may be normal, widened or narrowed. Vacuolation is seen at times in the head of the femur and in the trochanter. The angle of the neck of the femur is usually a little smaller than normal. The general appearance on roentgen examination is essentially similar in all cases.

Intrapelvic protrusion of the acetabulum was first described by Otto <sup>2</sup> in 1824 from a specimen in an anatomic museum. It has since been described under various names, often as related to the factor considered causative.

Pomerantz,<sup>3</sup> in 1932 made a detailed and excellent study of intrapelvic protrusion. He reviewed the seventy-nine cases previously reported in the literature and added six of his own. Since then thirteen additional papers on the subject have been published, adding thirty-two typical cases. A résumé of the pertinent facts concerning these cases is given in table 1.

Valentine and Müller <sup>4</sup> in 1921 and Pomerantz <sup>3</sup> in 1932, reviewing the cases reported, divided them into instances of typical and of atypical involvement. This report is concerned only with the cases of the typical form, of which forty-one were reported from 1824 to the time of Pomerantz' paper in 1932. Since then, including the five cases herein reported, forty-three cases have been added, a total of eighty-four cases in the hundred and ten years since the condition was first described by Otto. The small number of reported instances suggests that the condition is uncommon. The larger number of recent cases, forty-three in two years, indicates that the condition was undoubtedly often unrecognized or not reported.

Henschen <sup>5</sup> in 1909 suggested the criteria for a typical case. The inner acetabular wall protrudes into the pelvis. The cavity is generally enlarged, particularly inward and upward. The head of the femur, essentially of normal contour, is displaced into the deepened acetabulum, thus producing a shortening of the extremity.

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2. Otto, A. W., quoted by Pomerantz.<sup>3</sup>

3. Pomerantz, Maurice M.: Intrapelvic Protrusion of the Acetabulum (Otto Pelvis), *J. Bone & Joint Surg.* **14**:663, 1932.

4. Valentine, B., and Müller, H.: Intrapelvine Pfannenvorwölbung (Pelvis Otto-Chrobak), *Arch. f. klin. Chir.* **117**:523, 1921.

5. Henschen, K.: Die zentrale oder intrapelvine Pfannenwanderung der Hüfte auf coxitisch-arthropathischer Grundlage, *Ztschr. f. orthop. Chir.* **33**:438, 1913.



TABLE 1.—Résumé of Reported Cases

Author	Date	Author's Case No.	Side		Sex	Age	Duration	Onset of Symptoms, Patient's Age, Years	Comment
			Symptoms	Röntgenogram					
Oldelhoff, I. A., and Netkatcheff, E. L.: Vestnik khir. 24: 87, 1931	1931	1	M	Bilateral	M	50	20 yrs.	30	Pain both hips 20 years; limp 10 years; motion restricted; coxa vara on right.
		2	M	Right	M	22	8 mos.	21	Sudden onset with pain and fever 8 months previously; in bed since; narrow joint space; deep, protruding acetabulum
Pomerantz: .....	1932	4	F	Right	F	40	2 yrs.	38	Erysipelas of right thigh 2 years previously; pain since; motion restricted in abduction
		1	M	Left	M	32	11 yrs.	21	Pain in left hip during convalescence from gonorrheal infection in 1921
		2	M	Left	M	44	1 mks.	44	Acute involvement; early roentgenograms too dark to determine if acetabulum was deep
		3	M	Left	M	31	8 yrs.	23	Pain in hip 2 weeks after attack involving gall-bladder in 1917
		4	F	Bilateral	F	41	1 yr.	43	Pain in sacro-illiac joints and hips for 1 year; left worse
		5	F	Bilateral	F	58	3 yrs.	41	Pain in hips, right knee and back for 3 years; worse past 18 months
Michaelis, L.: Arch. f. klin. Chir. 170: 241, 1932	1932	6	F	Bilateral	F	32	1½ yrs.	30	Slight pain for 18 months; worse in right hip past year
		1	F	Unilateral	F	21	6 wks.	20	Three years before examination injured left knee; six weeks before, right hip; swelling of both knees and right hip
Cary, M. A., and Bernard, L.: J. Bone & Joint Surg. 14: 631, 1932	1932	1	F	Left	F	37	12 yrs.	25	Milk leg after childbirth, then symptoms in hip
		2	F	Left	F	43	4 yrs.	39	Pain in left knee and hip; in bed 5 months; roentgen films showed both hips affected
Larje, H. S.: Röntgenpraxis 4: 880, 1932	1932	1	M	Bilateral	M	35	21 yrs.	11	Multiple arthritis at 11 years; recurrence at 17; pain and limited motion of hip since
Sinn, L.: Röntgenpraxis 4: 856, 1932....	1932	1	F	Bilateral	F	26	13 yrs.	23	
Berent, F.: Röntgenpraxis 5: 303, 1933....	1933	1	M	Right	M	57	21 yrs.	33	Fell 27 years previously; painful right hip, motion restricted
		2	M	Right	M	60	?	?	Clinical examination gave negative results; fell; roentgenograms showed condition
Silfverskiöld, N.: Acta orthop. Scand. nav. 4: 1, 1933	1932-1933	1	F	Bilateral	F	58	43 yrs.	15	Fell on sacrum at age of 15; sticking pains in hip since; right hip ankylosed; in left only slight adduction was possible
		2	F	Right protruded; left, deep	F	60	30 yrs.	30	Gradual onset of pain and restriction of motion

Reed, E. N.: J. Bone & Joint Surg. 15: 502, 1933	3	55	M	Bilateral	Right protruded; left, deep	R. 35 yrs. L. 32 yrs.	20 23	At the age of 20 condition diagnosed as tuberculosis of right hip; three years later pain in both hips, with limited motion
Malcolmson, G. H., and Malcolmson, P. H.: Canad. M. A. J. 29: 181, 1933	5	42	F	Left	Unilateral	4 yrs.	38	One year after salpingitis sudden pain in left hip years; right hip tired when at school; severe generalized osteo-arthritis
Golding, F. C.: Brit. J. Surg. 22: 56, 1934	1	64	M	Bilateral	Unilateral	6 yrs.	18	Three rheumatic attacks between ages of 4 and 8 since age of 18
	1	62	F	Right	Bilateral	Many years	..	Generalized osteo-arthritis
	2	40	F	Bilateral	Bilateral	R. 47 yrs. L. 4 mos.	15 61	Pain in right knee and back 20 years; no pain in right hip; pain in left hip 4 months
	3	33	F	Bilateral	Bilateral	9 yrs.	31	Motion of hip restricted at age of 16 and pain occurred at 32
	4	42	M	Left	Left	4 mos.	33	Gonorrheal infection 8 weeks before pain began
	5	63	M	Bilateral	Bilateral	18 yrs.	24	Gonorrhea, 1904 to 1909
	6	64	M	Right	Bilateral	R. 4 yrs. L. 17 yrs.	R. 59 L. 46	Gonorrhea at age of 20
	7	67	M	Bilateral	Bilateral	44 yrs.	59	Gonorrhea in 1925; symptoms after a fall 8 years before examination
Gellman, M.: South. M. J. 15: 802, 1933	9	67	F	Left	Unilateral	10 yrs.	34	Marie-Strümpell spine for 20 years; hips painful for 10 years; roentgenograms showed typical intra-pelvic protrusion
	10	76	F	Right	Unilateral	1 yr.	66	Arthritis of left knee and right wrist 1 year; roentgenograms showed typical intra-pelvic protrusion
Nichols, B. H., and Schifflett, E. L.: Am. J. Roentgenol. 31: 346, 1934	1	26	M	Right	Right protruded; left, deep	1 yr.	75	Gross dental sepsis; pain and swelling left wrist 1 year; roentgenogram showed typical intra-pelvic protrusion
	2	15	F	Right	Right	11 yrs.	25	Acute gonorrhea in 1931; major involvement right hip; left acetabulum deep
Schnap 12	1	50	M	Bilateral	Bilateral	10 yrs.	4	Diagnosed in 1925 as Perthe's disease; roentgenogram showed bulge of inner acetabular wall; hypertrophic polyarthritis for early symptoms
	2	67	F	Bilateral	Left protruded; right, deep	10 yrs.	40	Eleven pregnancies, 2 miscarriages for 12 years; left hip stiff; right free motion
	1	34	M	Bilateral	Bilateral	2 yrs.	32	Chronic gonorrhea
	2	45	F	Left	Left protruded; right, deep	6 yrs.	39	Chronic gonorrhea; roentgenogram showed left protruding and deep right acetabulum

## REPORT OF FIVE CASES

CASE 1.—E. C., a white woman aged 69, was admitted to the hospital on Sept. 30, 1933, and was discharged on Nov. 8, 1933. The diagnosis on admission was fracture and dislocation of the left shoulder and fracture of the pelvis. An added diagnosis on discharge was intrapelvic protrusion of the acetabulum.

The patient stated that her father, three sisters and three brothers were all similarly misshapen (back and hips) but that she was the least deformed. They all walked awkwardly.

The patient was admitted to the hospital for the treatment of injuries resulting from an automobile accident. On roentgen study an intrapelvic protrusion of the head of the femur was noted.

Examination during convalescence, on Nov. 4, 1933, showed that the patient walked awkwardly. She said her gait had always been the same but that she had no pain. Examination of the trunk showed a mild dorsolumbar rotary lateral curvature to the right. Pressure on the pelvis was not painful. The range of motion is given in table 2. Examination of the joints, other than the hip, gave negative results. The length of the extremities was equal.

Roentgen study on admission of the patient to the hospital showed a fracture of both pubic bones and an impacted fracture of the surgical neck of the left humerus, with partial dislocation of the head. There was an intrapelvic protrusion of the left acetabulum and a deep right acetabulum, not associated with the recent accident. Subsequent roentgen ray examination showed good healing of the several fractures.

Roentgen examination was made on Nov. 6, 1933 (fig. 1 A).

*Comment.*—This patient, aged 69, was married and had two children. Roentgen examination showed an intrapelvic protrusion of the left acetabulum and a deep acetabulum on the right side. The general appearance of the hip joints, aside from the protrusion, was essentially the same. The hips had always been symptomless as regards pain.

The patient stated that eight members of her immediate family had similar disabilities of the trunk and hips and walked as she did. Those living were in Germany, and examinations were unattainable. The condition of the hip was ascertained when the patient was examined for a fractured pelvis.

CASE 2.—T. R. was a Negro aged 61 years.

The patient stated that his maternal grandfather, his mother, an uncle, a sister and one cousin all had the same trouble with their extremities as he had. Those surviving were a cousin (case 5 in this paper) and a sister, who refused to be examined or to have roentgenograms made because she was a Christian scientist. All walked awkwardly and had pain referred to the extremities.

The patient was examined during November 1932. He stated that his gait had always been awkward and that he had had intermittent pain in the hips. As a child he could not run as other children did. At the age of 8 years, the doctors said that he had "some sort of hip trouble." When he was 10 years old, he walked with crutches and wore a brace on the left lower extremity and a high shoe on the right foot. The disability gradually increased, and the trouble had been almost constant for twenty-five years. At times the hips seemed to lock. The back and the upper extremities were symptomless.

TABLE 2.—Range of Motion: Pertinent Data

Case	Age	Sex	Duration of Dis- comfort, Years	Patient's Limp or Age Arkwild Then, Years	Side	Attitude at Rest	Abduc- tion, Degrees	Adduc- tion	Range of External Rotation	Range of Internal Rotation	Flexion, Degrees	Exten- sion	Acetabulum
1	69	F	No pain on either side	..	Always	30° external rotation	40	Normal	Slightly restricted	20° external rotation	Normal	Normal	Deep
2	61	M	56	5	Always	Normal	20	Normal	Fixed 15°	Fixed 15° external rotation	70	Normal	Protruding
3	60	F	R. 27 No pain on left side	R. 33	22	23° external rotation; midposition	Fixed, mid- position	Fixed, mid- position	Fixed 20°	Fixed 20° external rotation	120	175°	Deep
4	45	M	R. 3 L. 36	R. 42 L. 15	On change of position	20° external rotation	10	Midline	Fixed 5°	Fixed 5° external rotation	80	165°	Protruding
5	54	M	R. 15 No pain on left side	R. 39	15	Midposition	Midline	Normal	Slightly restricted	20° external rotation	125	Normal	Protruding
						20° external rotation	Midline	10°	15°	Midline	75	Normal	Protruding
						5° external rotation	10	10°	25°	20° external rotation	70	Normal	Protruding
						Fixed 25° adduction; 15° external rotation; 15° flexion	..	Fixed 5°	Fixed 5° external rotation	115	Normal	Normal	Protruding
						45° external rotation	Normal	Normal	Fixed 45°	Fixed 45° external rotation	135	Normal	Protruding
									.....	.....	.....	.....	Slightly protruding

Examination on Nov. 21, 1932, showed that the patient walked with a knock-kneed attitude. The range of motion is shown in table 2. The knees and feet were normal on examination. The deep reflexes were all normal.

Roentgen examination was made on Jan. 19, 1934 (fig. 1 *B*). Films made on Sept. 17, 1930, more than three years previously, showed a somewhat similar pic-

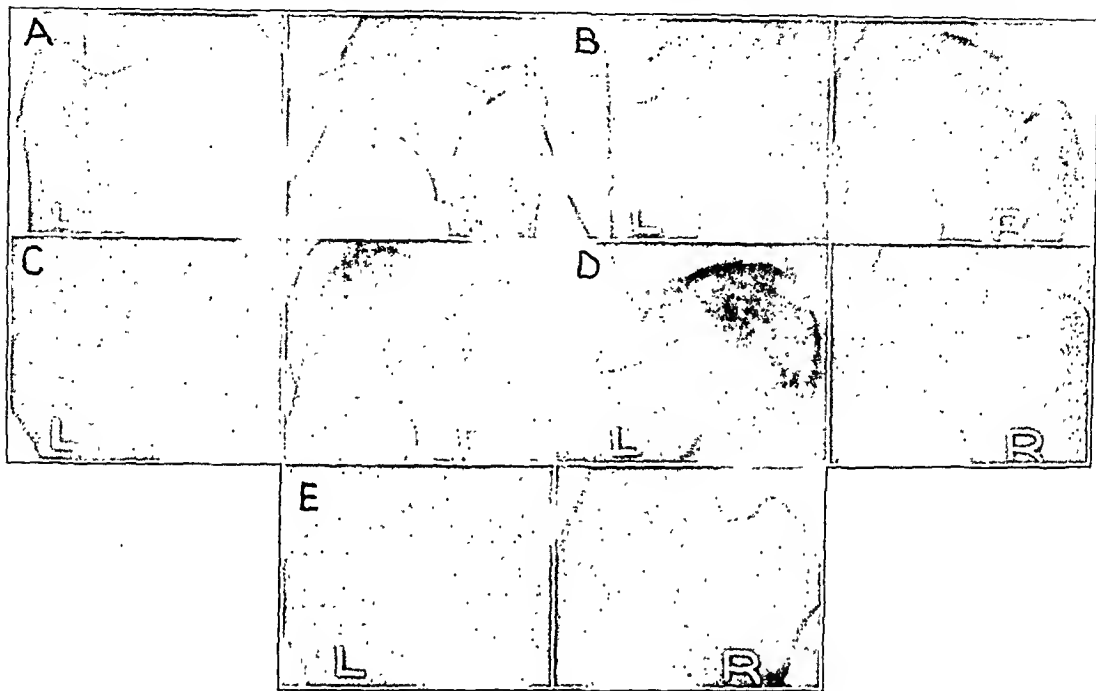


Fig. 1.—*A*, case 1. A woman aged 69 had no pain but had had an awkward gait since childhood. The left hip shows spurs and a dome-shaped head of the femur. The joint space is defined, and there is slight protrusion. On the right is a deep acetabulum. *B*, case 2. A man aged 61 had bilateral intrapelvic protrusion. He had had an awkward gait since childhood. The heads of the femurs are eroded. There are vacuolated areas in the head of the right femur and in both trochanters with marginal spurs. The head of the right femur is dome-shaped, and the joint space is slightly narrowed. The cavity is deep. The left acetabulum is widened, and there are inward protrusion and hypertrophic changes. *C*, case 3. A woman aged 60 had bilateral intrapelvic protrusion. There had been pain in the right hip for twenty-two years but none in the left. The heads of the femurs are intact. On the right the joint space is more narrowed and the head of the femur is slightly dome-shaped, with spurs. The great trochanters approximate the pelvis. There is marked protrusion on the right but less on the left. *D*, case 4. A man aged 45 had bilateral involvement. The left hip became painful at the age of 15 years, the right at 42. The femurs show intact dome-shaped heads and marginal spurs. On the right the space is slightly narrowed, the cavities are widened, the inner wall protrudes and the heads are larger. On the left the cavity is deep. *E*, case 5. A man aged 54 had bilateral involvement and had had an awkward gait always. Pain appeared in the right hip at the age of 39 years, but there was no pain in the left. The femurs have intact dome-shaped heads. The joint spaces are narrowed. There is acetabular protrusion and the cavities are deep and wide. On the left there are marginal spurs. On the right the head of the femur is eroded.

ture, except that the erosion had not occurred in the head of the left femur and the joint space was slightly narrowed. There were no vacuolated areas in the heads of the femurs.

*Comment.*—Although the patient had a positive Wassermann reaction, the history of a so-called similar condition in the family, the symptom of a disability of the hip since early childhood and the appearance of the hip joints on roentgen examination suggest the possibility of hereditary involvement and of a congenital lesion with a developmental defect in the hip joints.

CASE 3.—G. U., a white woman aged 60, was referred to me by Dr. Leon Solis-Cohen.

The patient had sprained her right ankle twenty-seven years before admission and had since had discomfort in that extremity. The pain gradually radiated to the knee and the hip. She had a locking sensation in the right hip when attempting to stand or when flexing the trunk. When she was seen in February 1933, she had pain in the right hip, knee and ankle, which was worse on change of position and after exertion. The left ankle had been painful for four weeks, but she had no discomfort in the left knee or hip. She had had backaches for the previous six months only.

The deformity of the back had the appearance of an old rigid kyphosis of adolescence. The patient arose from her chair with difficulty and slowly straightened her trunk. She walked awkwardly and with a limp on the right side, with the body listed to the right and with the trunk flexed. The range of motion is shown in table 2. The knees and feet were normal. Examination did not indicate the cause for the symptoms, which had been referred to the right ankle for the past twenty-seven years.

Roentgen examination, on Jan. 21, 1932, of the spine, knees and ankles gave negative results. Study of the hips revealed intrapelvic protrusion (fig. 1 C).

*Comment.*—This patient was 60 years of age. She had had two children. The right hip was painful for twenty-two years, and roentgen examination showed typical intrapelvic protrusion. There was no discomfort referred to the left hip, but clinical and roentgen examinations revealed abnormalities similar to those of the right hip. The disability followed a sprained ankle, which, on examination, showed no abnormality. One must consider the preexistence of a lesion in the hip which made the part structurally weak as compared with the normal. The effects of strain and trauma caused the pain complained of in the extremity. There was no history suggesting that the condition was hereditary.

CASE 4.—A white man aged 45 years was referred to me by Dr. George Mandelbaum.

At the age of 18 years the patient fell from a bicycle, striking his left hip on a stone walk. For some years previous to that he knew that the left lower extremity functioned less well than its fellow and would tire. There was a gradually increasing disability of the left hip, beginning about a year after the fall. He was treated with rest in bed and with a plaster cast. The pain abated, but

motion of the hip was restricted. He had no pain or further discomfort in the left hip, except that he tired after exertion.

In February 1931 a car which the patient was driving struck a tree. His right knee struck the dashboard of the car, and from that time he had discomfort in the knee, a sense of weakness in the hip and pain and stiffness on change of position. He likened the discomfort to that suffered in the left hip twenty-five years before. *He had no backache.*

Examination of the upper extremities, head and neck gave negative results. At rest the trunk was normal, but on weight bearing it flexed slightly at the hips. The range of motion is shown in table 2. The feet and knees were normal.

Roentgen examination revealed abnormality of both hips (fig. 1 D).

*Comment.*—Since early adolescence the patient knew that his left hip was not as strong as his right. A year after a fall on the left hip he had discomfort and later stiffness. Twenty-four years later, at the age of 42, when he injured the right knee, he first had discomfort in the right hip. Roentgen examination showed similar lesions.

It hardly seemed likely that two hips involved at intervals of many years would show similar lesions on clinical and roentgen examination. The conditions found were evidently due not to trauma per se but rather to the effects of stress and strain on a preexisting malformation, perhaps congenital, of the involved part. There was no history suggesting that the condition was hereditary.

CASE 5.—H. C. was a Negro aged 54.

The patient was referred to the orthopedic clinic by his cousin (case 2), who stated that they had had similar disabilities since childhood. The patient had always walked awkwardly.

The family history was the same as that in case 2. The patient in case 2 is a maternal first cousin.

The patient was well until 1918, when he was 39. He then had an infectious condition of the right hip, which confined him to bed for eighteen months. The hip had since been painful. He also had constant pain in the knees and calves of the legs, worse on the left side. The left hip was not painful.

Examination on Jan. 26, 1934, showed that the patient stood with the body listed to the right and with the trunk flexed 20 degrees at the hips. His gait was awkward. With the feet in the same plane, the right heel was  $2\frac{1}{2}$  inches (6.3 cm.) off the ground. At rest the attitude of the back was normal. The range of motion is shown in table 2.

Examination of the right knee showed that motion was free but that the joint was distended with fluid. Motion of the left knee was normal. There was a moderate degree of structural weakness in both feet. There was a  $\frac{1}{2}$  inch (1.3 cm.) swelling of the right knee. The left lower extremity was  $\frac{3}{4}$  inch (0.6 cm.) longer than the right; the apparent lengthening was  $2\frac{3}{4}$  inches (5.7 cm.).

Roentgen examination was made on Jan. 26, 1934 (fig. 1 E).

*Comment.*—The family history was the same as that in case 2. The patient was ill for eighteen months in 1918, at the age of 39, and had had a stiff hip since. However, he had had an awkward gait since early childhood. On roentgen study and on clinical examination it was noted that both hips were involved. The possibility that the condition was hereditary was similar to that in case 2.

## DEVELOPMENT OF THE ACETABULUM

The acetabulum develops from three primary centers (fig. 2), one for each of the three main bones of the cavity. These appear between the third and the sixth fetal month.<sup>6</sup> The bones of the acetabulum are joined by a Y cartilage, the os acetabuli, which has a secondary center of ossification appearing at about the age of 11 years. At that age the head of the femur grows very rapidly, and there appear the secondary centers of ossification for the acetabular rim, one each for the anterior, superior and posterior parts.<sup>7</sup> This rim gives added support to the rapidly enlarging head. Fusion of the acetabulum is usually completed at about 17 years of age.

The width and depth of the normal acetabulum are determined by the growth of the three main bones of the cavity, the connecting Y-cartilage and the three centers for the acetabular rim (fig. 3). The acetabulum varies in size and shape within a normal range as much as may any other part of the body; its average depth is 2.5 cm. Heredity undoubtedly has an important influence.

At birth the acetabulum may be divided into two equal parts, the iliac and the ischiopubic (fig. 2). With growth and weight bearing the ischiopubic area becomes relatively larger, and the proportion changes to 2:3. If the iliac portion lags in growth and/or with an overgrowth of the ischiopubic portion the upper part of the cavity is oblique, the marginal lip is poor and a small, shallow acetabulum results.<sup>8</sup> If the iliac portion overgrows and/or the ischiopubic portion is underdeveloped, a larger but also shallow cavity (fig. 3) results. The upper portion is also oblique. In both anomalies a greater strain is placed on the ligaments supporting the weight of the body.

These disturbances of development are associated with the congenital dislocations and subluxations. If, however, equal overgrowth occurs with a persistence of the infantile ratio of 1:1, a large, deep acetabulum is formed.

Another factor in the growth and depth of the cavity is the development of the acetabular rim. Retarded development may cause a shallow cavity, while overgrowth of the rim helps to produce the exaggerated or deep acetabulum. Lovett and Soutter<sup>9</sup> concluded that the acetabular

6. Piersol, G. A.: *Human Anatomy*, Philadelphia, J. B. Lippincott Company, 1907, p. 337.

7. Morrison, L. B.: *A Study of the Hip Joint from the Standpoint of the Roentgenologist*, *Am. J. Roentgenol.* **28**:484, 1932.

8. Cravener, E. K.: *Acetabular Decompensation*, *J. Bone & Joint Surg.* **16**: 618, 1934.

9. Lovett, R. W., and Soutter, Robert: *Congenital Dislocation of the Hip (Study of Two Hundred and Seventy-Seven Dislocations)*, *J. A. M. A.* **82**:171 (Jan. 19) 1924.



shelf is originally oblique but grows horizontal with the beginning of weight bearing. The shelf varies in effectiveness, being abnormal in about 10 per cent of persons. Congenital deformity exists if the generic

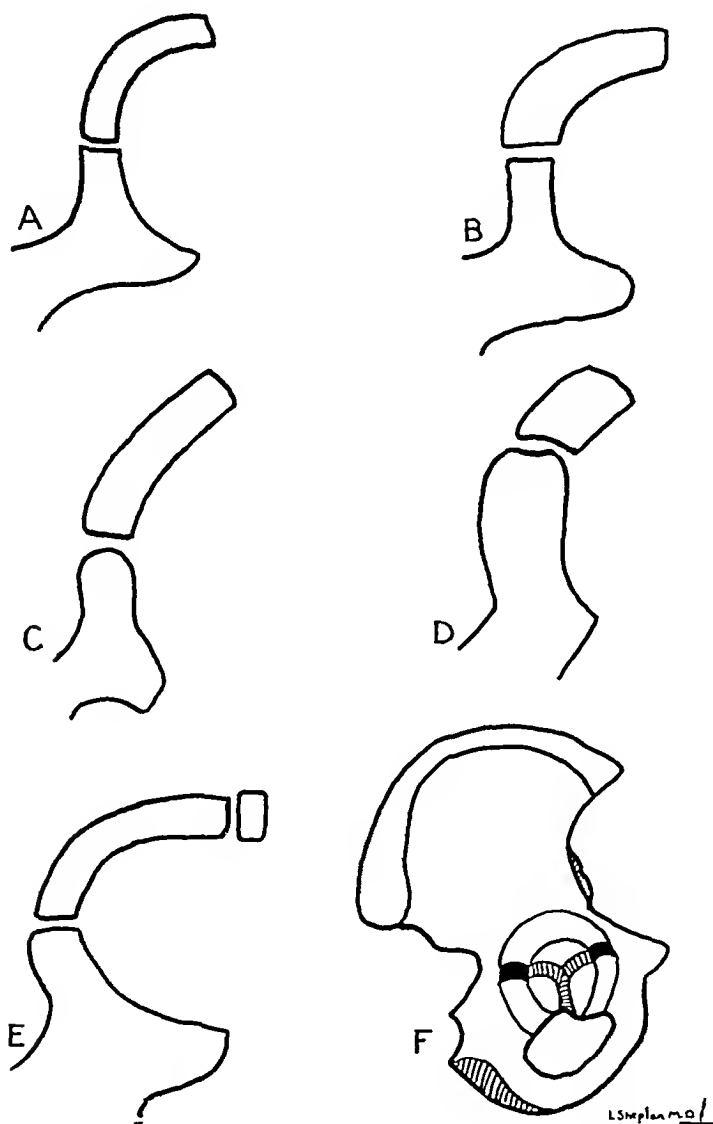


Fig. 2.—Normal and abnormal development of the acetabulum. *A*, normal acetabulum at birth. The structure is divided into two equal parts, the iliac and the ischiopubic, in a ratio of 1:1. *B*, normal acetabulum at a later stage, when the ratio of the iliac to the ischiopubic elements is 2:3. *C*, a large shallow acetabulum produced by overgrowth of the iliac and/or undergrowth of the ischiopubic elements. *D*, a small shallow acetabulum produced by overgrowth of ischiopubic elements and/or undergrowth of the iliac elements. *E*, a deep acetabulum produced by overgrowth of the iliac and of the ischiopubic elements and overgrowth of the rim, with persistence of the infantile ratio, 1:1. *F*, normal development of the acetabulum. These drawings were based on those presented by Cravener.<sup>8</sup>

centers either fail to develop or develop but fail to grow normally. In all congenital deformities deficient development is more common than overdevelopment. Cases of congenital dislocation and subluxation are, therefore, more common than cases of deep acetabulum from overgrowth.

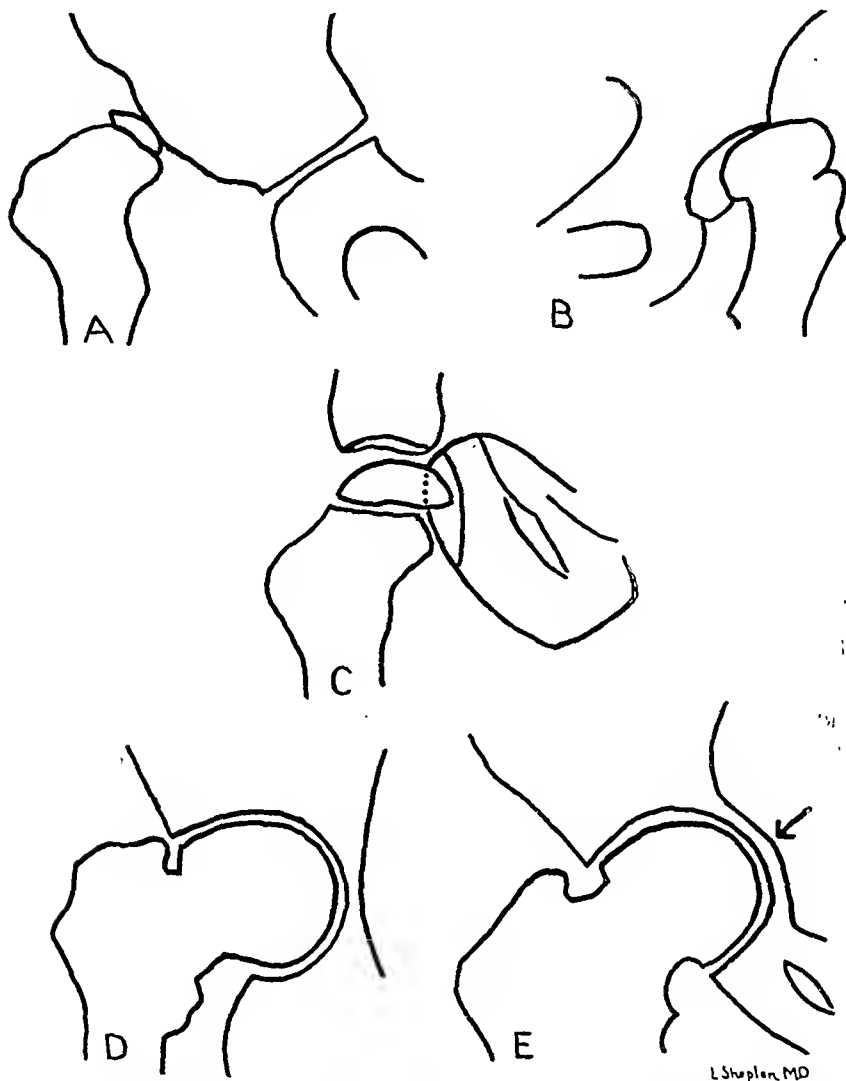


Fig. 3.—Depth of the acetabulum. *A* represents dislocation; *B*, subluxation; *C*, normal structure; *D*, a deep acetabulum, and *E*, intrapelvic protrusion. These drawings were based on those presented by Schaap.<sup>12</sup>

Le Damany,<sup>10</sup> discussing anomalies of the hip, stated: "The floor of the socket which is no longer acted upon by the pressure of the femoral

10. Le Damany, P.: Influence de la tête fémorale sur le creusement et la conservation de la cavité cotyloïde, *Trav. scient. Univ. de Rennes* 2:363, 1903.

head remains too thick, the socket itself consequently becomes too shallow and in most serious cases dislocation of the hip ensues." Conversely, the inner wall of a deep acetabulum is thin. The two thin or weak places normally in the os innominata are in the wing of the ilium and the cotyloid cavity. A deep acetabulum has even a weaker and thinner inner wall. This has been shown on roentgen studies of the affected hips.

Since the acetabulum is ossified at the age of 17, the occurrence of deformities, such as intrapelvic protrusion, almost symptomless as regards early pain and other major subjective disturbances, must precede the attainment of this age. A hip joint that is the site of a congenitally deepened acetabulum is weak when compared with a normal joint. Although the joint may appear stronger because of a large bony support, actually it is weaker, since with altered function there must be a disturbance of the normal mechanism of the joint.

In the mechanism for the production of intrapelvic protrusion of the acetabulum the prime factor is a preexisting deep acetabulum. There are an abnormal strain of dysfunction, due to a deeply seated head, and an altered relation of the pressure of the pelvifemoral muscles. These, together with the effects of weight bearing and perhaps disease, may account for the bulging and intrapelvic protrusion of the inner acetabular wall, its almost paper-like thinness and the molding of the head of the femur to the dome-shaped acetabulum, as may be seen on the roentgen films. The depth of the acetabulum may be increased to 5 cm. or more. Into the deepened acetabulum the head of the femur may be displaced until the greater trochanter approximates the side of the pelvis and the lesser trochanter the ischium. A change occurs in the lines of stress and strain in the head and neck of the femur, as well as in the acetabulum.

In patients with an intrapelvic protrusion of the acetabulum the angle of the neck of the femur is usually a little smaller than normal. Despite the theoretical consideration that this angle should be increased in causing an intrapelvic protrusion, the opposite is found. The inner acetabular wall is often seen to be sclerosed. This indicates the reaction of the tissue to stress and strain of pressure from the head of the femur on the potentially weak, thin inner wall of the socket. Roentgen studies show an absence of sclerosis in the ilium adjacent to the superior part of the acetabulum, where it might be expected because of pressure from the femur with the angle of the neck less than normal. It would seem, therefore, that the condition of intrapelvic protrusion is developmental and is engrafted on a congenitally deep acetabulum during the period of active growth and before fusion occurs.

Few cases of intrapelvic protrusion have been reported in patients under 20, (twelve of eighty-four reported cases of typical involvement). There are relatively firm bony support and stability in a large acetabulum.

Subjective effects of irritation and stress and strain are not manifested early, as they are readily compensated for. Later, irritation may occur with the fusion and perhaps overgrowth of the acetabular rim and the approximation of the trochanters to the side of the pelvis, and also as the result of irritation from trauma and infection. Late symptoms may be associated with the changes incident to the degenerative stage of life, after 40, and the presence of any condition lowering the patient's general resistance.

The factors responsible for the subjective complaints, usually in adult life, are concerned with the minor changes seen on the roentgen films of patients with intrapelvic protrusion of the acetabulum. Some of these are the variations in density of the bone, the width of the joint line and vacuolation. The major features in the roentgen pictures of the involved hips are essentially similar.

On reviewing the illustrations of previously reported cases a deep acetabulum or one showing a slight protrusion of the inner acetabular wall into the pelvis was seen at times on the side described as normal. This suggests that minor changes in the interpretation of the roentgen films as to the depth of the acetabulum may have been ignored.

The cases reported have been classified symptomatically as those of chronic and those of acute infectious involvement. It is possible that the acute condition is engrafted on a previously deep acetabulum. The chronic type is more common and occurred in the five cases herein reported. In the second case described by Pomerantz<sup>3</sup> the condition seems to conform to the criteria for the acute variety. He described the pathologic change as primary involvement of the acetabulum, with softening, so that muscle spasm and weight bearing displaced the socket and the head of the femur inward.

#### REVIEW OF THE LITERATURE

Many etiologic factors (about sixteen) have been suggested. Otto stated that the condition is an abnormal manifestation of gout. It has since been ascribed to arthritic processes of various etiology, and also to syphilis, malignant disease, metabolic and endocrine disorders, osseous and chondral irritation and trauma. The condition has previously been considered the end-result of an inflammatory or degenerative process within the hip joint. The symptoms in most of the reported cases began in adult life and were usually not sufficiently severe to account for the changes shown on the roentgen films. The many etiologic factors suggested were therefore probably only the irritating agents acting on an area of potential weakness.

Eppinger<sup>11</sup> studied four anatomic specimens. He attributed the pathologic process to a disturbed growth in the cartilage of the

11. Eppinger, quoted by Pomerantz.<sup>3</sup>

acetabulum, of the nature of a malacia or chondrodystrophy—a developmental anomaly of the acetabulum in which the cartilage did not ossify but was projected into the pelvic cavity.

Schaap<sup>12</sup> expressed the opinion that in cases of chronic involvement connection with any disease should be denied. He stated that the lesion occurs mainly in women, is more often bilateral and shows practically the same picture in each case. He concluded that the condition is due to congenital deformity of the acetabulum.

A résumé of the cases of the typical form reviewed by Pomerantz showed that twenty-eight of the patients were over 20 years of age, two were less than 20 years old and for eleven the age was not given. Thirty-two were women, seven were men and the sex of two was not given. The duration of symptoms referable to the hip was not discussed.

Thirty-eight cases of the typical form have been reported in the literature since Pomerantz published his paper in 1932 (table 1). Thirty-seven of these patients were over the age of 20. There were twenty women and eighteen men. Symptoms were referred to the involved hip by nine patients before the age of 20; one never had discomfort, and in twenty-eight the symptoms began after the age of 20. Five cases of bilateral involvement are reported in this paper; all the patients were over 20, and three were men. Four of the ten involved hips had never been painful. Two of the patients had pain, at the ages of 5 and 15 years, respectively.

#### SUMMARY

The etiology of protrusion of the acetabulum, in my opinion, is primarily a congenitally deep acetabulum, which is basically the result of overgrowth of some elements of the acetabulum. This may be hereditary, as was suggested by three histories in five cases personally observed. The intrapelvic protrusion was an acquired defect superimposed on a deep acetabulum. The symptoms of discomfort began only after trauma due to stress and strain of function, infection or injury had so aggravated the condition as to cause a clinical picture of arthritis or of a derangement in the hip joint.

Roentgen examination showed bilateral involvement of the hips in all five cases. If arthritis were the fundamental etiologic factor, bilaterality would be unusual in this group, and more joints would undoubtedly have been involved.

Ossification of those portions of the ilium, ischium and pubis which form the acetabulum is usually completed at the age of 17 years. The typical deep acetabulum with intrapelvic protrusion must therefore have

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12. Schaap, C.: Intrapelvic Protrusion of the Acetabulum, *J. Bone & Joint Surg.* **16**:811, 1934.

been present previous to that time. The symptoms in the right hip in case 3 did not begin until the age of 32; there was no discomfort on the left side although roentgen examination showed that both hips were typically involved. In case 4 the patient had symptoms referred to the left hip in early adolescence, but the right hip was not painful until he was 42 years of age, and the development of symptoms followed an injury to the knee. The remaining three patients had had peculiar gaits since walking began.

All roentgenograms showed the same major changes, which were not altered by the exciting cause for the discomfort or the time of the onset of the symptoms. The roentgen pictures have a characteristic appearance.

TABLE 3.—*Résumé of Cases Typical of the Form Reviewed*

Reviewed	Cases	Age of Patient			Sex			Duration of Symptoms in Hip		
		Over 20	Under 20	?	M	F	?	Over 20	Under 20	No Discomfort
Pomerantz <sup>3</sup> (23 authors).....	41	28	11	2	7	32	2	Not discussed		
Rechtman (14 authors).....	38	37	1	0	18	20	0	28	9	1
Rechtman.....	5	5	0	0	3	2	0	2	2	4 hips, 3 patients
Total.....	84	70	12	2	28	54	2	30	11	

A history not alone of the present attack but of the first symptoms referable to the hip may suggest the congenital etiology of the condition. A study of the family history may show the relationship of heredity.

#### CONCLUSIONS

Five cases of congenitally deep acetabulum and of intrapelvic protrusion of the acetabulum are presented. In all the lesions were bilateral. Two of the patients were women who delivered children with no undue difficulty despite the undoubted narrowing of the pelvis by the deformity. Of the ten hips, six were painful at some time and four caused no discomfort. Seven of the ten hips were essentially similar in appearance on roentgen examination. The other three hips showed deep acetabula without intrapelvic protrusion.

Three of the family histories suggested a hereditary factor.

A consideration of the embryology and of the development of the acetabulum further suggests that the condition is congenital.

The adoption of one term for general use in the nomenclature is advised.

# DIAGNOSIS OF CANCER OF THE STOMACH

## THE USE OF THE GASTROSCOPE AND THE GRUSKIN TEST

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The lesion causing approximately half of the deaths from cancer and 3 per cent of all the deaths in this country, with a mortality rate that increases in spite of continued study, cannot be overstressed. Fair advances are being made in the attack on the problem of cancer in general. Cancer of the stomach practically alone remains with an increasing death rate. The reason is at once apparent. The incidence is high, and the diagnosis is perhaps the most difficult one to make at the present time. The symptomatology is so variable as to be often valueless, and particularly is this true in the early stage when the cancer is eradicable. While roentgen diagnosis of the cancer has been greatly improved, the dependence on this very procedure perhaps contributes as much to the incidence of advanced cases as any other factor. The difficulty of arriving at a definite diagnosis by clinical methods and the fear of submitting the patient to a needless operation have caused physicians to place undue reliance on roentgenograms, with the result that many patients with early cancer and symptoms arousing suspicion of cancer are given a clean bill of health and carcinoma eliminated from consideration, to the subsequent regret. I feel safe in saying that there is no true early diagnosis of carcinoma of the stomach from roentgenograms. The size of the organ and its structure, with its various normal folds and rugae, its *magenstrasse* and its sensitivity to intrinsic and extrinsic stimuli, make the detection of a small lesion uncertain. Only when there is a constant filling defect or sufficient change in the wall to cause a persistent shadow or an obstruction may a presumptive diagnosis of cancer be made, and usually at this time the lesion is advanced.

The increase in the incidence of carcinoma of the stomach is perhaps more relative than absolute. The fact remains, however, that about 45 per cent of all deaths from cancer in men are due to the lesion in the stomach, and, while in women the genital tract is most often the primary site, the stomach is the locus in over 20 per cent of the cases

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thus closely following the uterus and the breast. Cramer's<sup>1</sup> figures show a gross European incidence of 52 per cent, Bavaria having the highest with 55.8 per cent and England the lowest with 25 per cent; these figures include both sexes. The racial character of the incidence is striking and may lead one to overstress the factor of heredity. Stevenson's<sup>2</sup> work in England carried knowledge of the environmental distribution further by showing an increasing percentage of cancers of the stomach occurring in the lower strata of society, suggesting a difference in alimentary hygiene as the basis for the variation. That there is a racial or social (hygienic) susceptibility is further evidenced in the report from Sumatra, where the population is composed of Chinese and Javanese, races that never intermarry, and where primary cancer of the liver is common. The statistics show primary carcinoma of the liver occurring in 36 per cent of the Chinese and 54.4 per cent of the Javanese and new growth in the stomach in 25.3 per cent of the Chinese and only 1 per cent of the Javanese.

How serious the problem of early diagnosis has become may be realized from a personal observation made in a very active surgical service in a neighboring city: In four years there were seen on the operating table only four patients who fulfilled all of the requirements for operability. In comparison with this incidence, the records on the last one hundred patients with cancer of the stomach who were operated on at the New York Post-Graduate Medical School and Hospital were examined. Taking as criteria the classic requirements according to leading textbooks of surgery,<sup>3</sup> namely, a relatively small growth which is freely movable and which is unaccompanied with evidence of metastases or with ascites or with anemia due to the growth (less than 60 per cent hemoglobin), one found that 1 per cent of the patients had growths that were definitely operable; in 24 per cent there was some question as to the operability, thus leaving 75 per cent of the patients potentially incurable. Seventy-five per cent had metastases, while in 25 per cent either there were no metastases in the section removed or metastases were not felt at the time of operation. The common use of the words "operable" and inoperable" is unfortunate. The term "potentially curable" would be more accurate. The teaching in surgery today should be that, with or without metastases, operation should be performed if at all possible, because if there is no operation the condition is hopeless. On the other hand, removal of the parent

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1. Cramer, W.: Cancer of the Stomach, *Lancet* 1:1 (Jan. 6) 1934.

2. Stevenson, quoted by Rowlands, R. P.: Cancer of the Stomach, *Brit. M. J.* 1:905 (May 27) 1933.

3. Babcock, W. W.: *Text-Book of Surgery*, ed. 2, Philadelphia, W. B. Saunders Company, 1935; Personal communications to the author. DaCosta, J. C.: *A Manual of Modern Surgery*, Philadelphia, W. B. Saunders Company, 1933.



growth in an apparently incurable stage often has a palliative effect even in the presence of metastases, with an occasional retrogression in these growths. Then, too, there is the possibility of a mistaken diagnosis or of an error as to the stage of advance and, as Balfour<sup>4</sup> said, once in a while one is fooled by seeing a patient concerning whose condition the prognosis was very bad survive and live a subsequently useful life for ten or more years.

For the last three years, according to the *Quarterly Cumulative Index Medicus*, an average of 104 articles on carcinoma of the stomach have been published each year. Analysis shows that 35 of the articles are in American journals, and that only one sixth of these are concerned with diagnosis, the real problem in cancer. The majority contain discussions of different methods of therapy—mostly new and larger resections for larger and more advanced growths. As there is only one cure for the condition, that is, early and complete resection, it seems that time and study are being wasted in devising more complicated operations, when the ones available are efficacious in trained hands when the lesion is curable.

Important points in the diagnosis should be discussed from time to time to keep the matter constantly in mind. In general it may be said that any person with symptoms of epigastric distress or uneasiness, whether associated with the digestion of food or not, should be regarded with suspicion, especially if this distress is of recent origin. The signs of cancer listed in textbooks—loss of weight, loss of strength, anemia, a mass in the epigastrium, vomiting of material like coffee grounds and tarry stools—together with a roentgen diagnosis, might be better classed as signs of incurability and impending death rather than as signs of carcinoma. This symptomatology was developed from the autopsy table, and it is well to keep the association of these signs with the autopsy table in mind. The clinical diagnosis is made more difficult by the fact that the signs may develop in one of three ways: 1. There may be an abrupt onset of epigastric distress, usually of a few weeks' or months' duration, with rapid development of an inoperable growth. This type of growth under the microscope is most often graded 4 or 3 in the Broder scale of malignancy. 2. There may be a gradual onset of epigastric distress, often relieved by food or soda for a time and variously diagnosed as gastritis, duodenitis, chronic cholecystitis, and peptic ulcer by the modern gastro-enterologist, who uses these terms to replace the cover-all of "dyspepsia" of his predecessor. 3. In the smallest group of patients there may be no symptoms referable to the gastro-intestinal tract until late in the course of the disease. It is this

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4. Balfour, D. C.: Curability of Cancer of Stomach, Surg., Gynec. & Obst. 54:312 (Feb.) 1932.

great variation in the kind and degree of symptoms that makes the labeling of cancer of the stomach difficult. The history, while seldom pathognomonic, is helpful and has served its purpose if it has aroused one's suspicion. While many patients lose "curable time" trying neighbor's suggestions and home remedies, it is more often one's own inability to confirm the diagnosis that leads to the hopeless condition seen so often at the operating table. In a review of a hundred charts of patients with cancer of the stomach in Philadelphia, 65 per cent were found to give a history of over six months' care at a clinic or at home by a physician for "stomach trouble." This means that six months' time was lost to the patient not through his own fault but through the ignorance of the medical profession. It seems certain that in gastro-enterologic clinics throughout the country, private and free, many early carcinomas are being treated under various diagnoses other than that of cancer. Obviously, all of the patients cannot be explored to find an occasional early malignant condition; thus one is led back to the primary conclusion that better methods must be found. Fortunately, this diagnostic field seems to be enlarging, and two of the added procedures will be further discussed.

The presence of achlorhydria in certain cases of carcinoma of the stomach has suggested a test for use as an adjunct in diagnosis, but as Comfort and Vanzant<sup>5</sup> concluded, the test usually fails when most needed. It may help to differentiate duodenal ulcer and a pyloric carcinoma, but it is subject to error. This brings me to the subject of ulcer. There must be a careful differentiation in the treatment of duodenal and gastric ulcer. A duodenal ulcer may be regarded passively with impunity, but a gastric ulcer is always dangerous owing to its potentially malignant character. Bloomfield's<sup>6</sup> recent report seems to indicate that cancerous ulcers have not been malignant from their onset but have developed from benign to malignant lesions over a period of time. It seems logical that if progress is to be made in the prevention of cancer of the stomach all gastric ulcers should be operated on, not for the removal of the ulcer per se but to eliminate the possibility of malignant growth. Any ulcer over 1 cm. in diameter, as has been shown, is more often malignant than benign, and the size of an ulcer as measured by means of the roentgen ray is notably inaccurate. The main thought, however, is that an ulcer in the duodenum is in an area free from the potentiality of cancer, while an ulcer in the stomach is in the organ most often the site of new growth. While the surgeon is prone

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5. Comfort, M. W., and Vanzant, R. R.: Gastric Acidity in Cancer of Stomach, *Proc. Staff Meet., Mayo Clin.* 8:271 (May 3) 1933.

6. Bloomfield, A. L.: Early Cancerous Changes in Peptic Ulcer, *J. A. M. A.* 104:1197 (April 6) 1935.

to abandon the treatment of duodenal ulcer to the physician, it is the belief that gastric ulcer necessitates a much more thorough investigation and, in the presence of reasonable doubt, an exploration. Only in this way can one make inroads into the alarming mortality from cancer of the stomach. While the figures for the immediate mortality from gastric resection are high (approximately 10 per cent in trained hands) one must remember that most resections today are made on advanced growths, in patients who present poor risks. In subjects who present good prospects, taken before the stage of hopelessness, the risk could be materially lessened, as shown in the reports on resections by surgeons who perform them as a routine in the treatment of peptic ulcers. Suggestions as to further diagnostic procedures seem quite in order, and I wish to make two.

At the present time carcinoma of the rectum is being treated successfully in more cases than is cancer of any other internal organ with the exception of that of the larynx, owing to the fact that in 85 per cent of the cases a growth in the large bowel is within reach of the finger or the proctoscope, and more physicians are making careful rectal and sigmoidal examination a part of their routine. What the proctoscope has meant in the diagnosis of rectal and sigmoidal lesions, it is my belief, the gastroscope will mean in that of lesions of the stomach. A great deal of work along this line is necessary, but with routine use replacing occasional use of the gastroscope in cases in which carcinoma is suspected the goal should be approached more quickly. Kussmaul (cited by Benedict <sup>7a</sup>) pioneered in gastroscopy, using a professional sword swallower as the subject of his experiments, but the results were far from satisfactory, Mikulicz <sup>8</sup> in 1881 and Rosenheim <sup>9</sup> in 1896 worked on the same procedure, but it was not until after 1900 that a satisfactory visualization was obtained. Subsequently, the apparatus was used considerably in Germany, but it was never used much in America, owing to its clumsiness and the elaborateness of the technic. Just three years ago, a German physician, Schindler,<sup>9</sup> and an instrument-maker named Wolf developed the Wolf-Schindler flexible gastroscope with its clever arrangement of lenses, and this instrument has revolutionized the work. The first American report, by Benedict <sup>7a</sup> of Boston,

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7. (a) Benedict, E. B.: Examination of Stomach by Means of Flexible Gastroscope, *New England J. Med.* **210:669** (March 29) 1934. (b) Benedict, E. B., and Allen, A. W.: Adenomatous Polypi of the Stomach, *Surg., Gynec. & Obst.* **58:79**, 1934.

8. Jackson, Chevalier, and Jackson, C. L.: Personal communication to the author; Peroral Gastroscopy, *J. A. M. A.* **104:269** (Jan. 26) 1935; *Bronchoscopy, Esophagoscopy and Gastroscopy*, Philadelphia, W. B. Saunders Company, 1934.

9. Schindler, R.: Ein völlig ungefährliches flexibles Gastroskop, *München. med. Wchnschr.* **79:1268**, 1932.

based on a study of seventy-five patients, demonstrated both the safety and the practicability of the use of this instrument. While Benedict<sup>7a</sup> used it particularly in the study of gastritis, its efficacy in the diagnosis of carcinoma is shown by the fact that in ten of twelve cases of cancer the condition was recognized, and in the first series of patients. Jackson's<sup>10</sup> results in Philadelphia were equally encouraging. It is easy to see that with improvement in the technic and especially with the advantage of experience in the recognition of the lesion the percentage of correct diagnoses will approach 100. Naturally there are objections. The gastroscope is still a highly specialized instrument, but in time the clinician will resort to the gastroscopist more and more in the diagnosis of lesions of this type. The idea is presented again to stimulate thought on the subject and to show a bright point in an otherwise dark outlook.

The other point that I wish to stress is along the line that many believe will eventually lead to the etiology of cancer, namely, sensitization. I refer specifically to the Gruskin<sup>11</sup> test for malignancy. There have been many tests for malignancy, but none has stood the test of time with such remarkable validity as the Gruskin test. It is based on the fundamental consideration that malignant cells are born embryonic and remain embryonic in contradistinction to normal cells, which are born embryonic but which mature. The protein of malignant cells is not the same as that of normal cells. This is shown chemically by the fact that incineration of malignant growths gives a heavy deposit of inorganic salts similar to the heavy deposit found after incineration of embryonic cells, while normal cells or benign growths when incinerated leave no such deposit or only a trace of inorganic salts. Biologically, the difference between embryonic and mature cells is shown by the fact that the fetus in utero is never attacked by the spirochete of syphilis until after the first six weeks or until the embryonic cells actually begin to mature and the character of their protein to change. The immaturity of the malignant cells and the specificity of their proteins are manifested by the formation of pseudopodia when the cells are injected intradermally and by the precipitation of the proteins by serum from persons with malignant growths. Thus the test is based on injection of an embryonic antigen made from the most embryonic cells known, namely, epithelial cells from the embryonic calves' pancreas or liver, for carcinoma, and, for sarcoma, Wharton's jelly, which contains the embryonic stellate connective tissue cells. While Gruskin's enthusiasm made his claims for his test sound exaggerated beyond the expectations of any laboratory procedure, later investigation has substantiated

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10. Jackson, C. L.: *The Use of the Flexible Gastroscope* (Address to New York Gastro-Enterological Society, 1935). Jackson and Jackson.<sup>8</sup>

11. Gruskin, B.: A Serum Test for the Diagnosis of Cancer Based on a New Theory of Etiology, *Am. J. M. Sc.* **177**:476 (April) 1929.

those claims. A careful clinical and serologic investigation by disinterested, and in some cases decidedly skeptical, observers showed positive results in 88 per cent of cases.<sup>12</sup> Since that time five more patients with positive Gruskin reactions and negative results from clinical examinations have shown the development of carcinoma, thus bringing the corrected percentage to 92.<sup>13</sup> Dr. Harry Bacon, in Philadelphia, in a series of fifty-one patients, had correct results with the Gruskin test in 100 per cent of the cases, and other observers have reported series with correct results in from 92 to 100 per cent of the cases. When one considers that the Wassermann test is accurate in only about 78 per cent of the cases, one realizes that in the Gruskin test one has something definite. It is not a cover-all diagnostic procedure. The Gruskin reaction is a very strong link to add to the chain of suspicious evidence that may lead to an early exploratory operation. It would be wise to make such a test on every patient who comes to a gastro-enterologic clinic and then carefully examine those with positive reactions with the thought of gastroscopy and exploratory operation in mind. It is clear that only in some such way will one discover the condition when a cure is possible.

One hundred patients were studied in cooperation with Dr. B. Gruskin. An analysis of the results follows:

Patients	Correct Results from Gruskin Test	Incorrect Results from Gruskin Test	Percentage of Correct Results
100	92	8	92
Positive Gruskin Reactions	Negative Gruskin Reactions	Percentage Correct Positive Gruskin Reactions	Percentage Correct Negative Gruskin Reactions
74	26	81.8	76.9

These figures show that the positive reaction to the Gruskin test did not agree with the result of clinical observation in eight instances. Some of these eight patients may later show clinical evidence of malignant change. While more observation on the possibilities of the Gruskin test is necessary before one may advocate its acceptance over clinical judgment, the results so far are extremely encouraging.

The possibility of further education of the public is far from exhausted. The effect of an educational campaign was well shown in the large number of patients with growths of the breast who presented themselves after the campaign of a few years ago. The traveler reading the miles of bill boards extolling the virtues of this or that tooth paste over others must pause and consider the great common good that could

12. Bacon, Harry E.: Gruskin Test in Carcinoma of Rectum, Anus and Colon, *Tr. Am. Proct. Soc.* **34**:149, 1933.

13. Gruskin, B.: Personal communication to the author.

be done by a campaign, national or international in scope, embracing bill boards, publications and the radio, and detailing the symptoms of early cancer, perhaps those of cancer of a different organ each month. Such a campaign would be a challenge to the medical profession to diagnose the lesions earlier and would greatly stimulate diagnostic research. While the scientific world struggles to find a cure for cancer it is at times refreshing to realize that there is a positive cure at hand in complete surgical removal. Perhaps more progress would be made if the cry were not, "When will we find a cancer cure?" but rather "When will we find an early diagnostic procedure?" With this thought in mind, cancer does not seem so hopeless, and with more research directed toward diagnosis, leaving the treatment to surgeons and the small field amenable to radium and roentgen therapy to radiologists, definite progress may be made.

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# GASEOUS DISTENTION ASSOCIATED WITH MECHANICAL OBSTRUCTION OF THE INTESTINE

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In spite of the fact that absolute evidence has not been obtained as to the cause of the symptoms and death in cases of mechanical obstruction, some writers emphasize distention as a fundamental etiologic factor. The disturbed physicochemical balance of the body has been considered a contributing factor. Herrin and Meeks<sup>1</sup> have reported that the symptoms of dehydration, decrease in blood volume, loss of electrolytes, alkalosis and especially dechlorinization were really the basis for the cause of death in cases of obstruction and that these symptoms could be reproduced in experimental animals by distending a segment of intestine to a relatively high air pressure. Carlson<sup>2</sup> has produced a condition similar to simple obstruction by the same procedure. The remarkable results obtained by Wangenstein<sup>3</sup> by the use of continuous suction with a nasal catheter in cases of simple obstruction may be attributed either to the relief of distention or to the removal of accumulated gas and fluid. Burget<sup>4</sup> has prolonged the life of experimental animals by relieving the tension in obstructed loops of bowel by simple aspiration of their contents. Raine and Perry<sup>5</sup> attributed the distention not only to a blocking of the normal pathways of elimination but to

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1. Herrin, R. C., and Meeks, W. J.: Distention as a Factor in Intestinal Obstruction, *Arch. Int. Med.* **51**:152 (Jan.) 1933.

2. Carlson, A. J.: *Proc. Staff Meet., Univ. Minnesota Hosp.* **3**:419, 1932.

3. (a) Wangenstein, O. H.: Therapeutic Considerations in the Management of Acute Intestinal Obstruction, *Arch. Surg.* **26**:933 (June) 1933; (b) The Early Diagnosis of Acute Intestinal Obstruction with Comments on Pathology and Treatment, *West. J. Surg.* **40**:1, 1932. (c) Wangenstein, O. H., and Paine, J. R.: Nasal Catheter Suction Siphonage: Its Uses and the Technique of Its Employment, *Minnesota Med.* **16**:96, 1933.

4. Burget, G. E.; Martzloff, K.; Thornton, R. C. B., and Suckow, G. R.: The Closed Intestinal Loop: Observations on Dogs with Jejunal and Ileal Loops and Chemical Analysis of the Blood, *Arch. Int. Med.* **47**:593 (April) 1931.

5. Raine, F., and Perry, M. C.: Intestinal Obstruction, *Arch. Surg.* **19**:478 (Sept.) 1929.

the gradually increasing intra-intestinal pressure, which in turn stimulates secretion of fluid and gas and diminishes absorption. It is with these points in mind that a study of the gaseous distention occurring in association with simple mechanical ileus is presented.

#### REVIEW OF THE LITERATURE

In discussing the origin of gas in the intestine the majority of observers state that the gas is derived from three sources:

1. Decomposition of intestinal contents
  - (a) Chemical and enzymic decomposition
  - (b) Bacterial fermentation and putrefaction
2. Diffusion of gases from the blood into the intestinal lumen
3. Passage of atmospheric air from the stomach into the intestine

*Chemical Decomposition.*—According to Kantor and Marks<sup>6</sup> an enormous amount of gas may originate in the upper portion of the small intestine. It is formed by mixture of the acid gastric contents with the carbonates present in the alkaline biliary and pancreatic secretion and is composed almost entirely of carbon dioxide. Von Bunge<sup>7</sup> emphasized that as much as 6 liters of gas may arise from this source. Schierbeck,<sup>8</sup> in studying the formation of gas in the stomach before and after ingestion of food, found that the carbon dioxide tension rose from 30 to 40 mm. before eating to 130 mm. two hours after digestion of food. He attributed this to the liberation of carbon dioxide by the synchronous secretion of sodium bicarbonate and hydrochloric acid from the mucous membrane. Kraus-Ragins<sup>9</sup> studied the liberation of ammonia in tryptic and peptic digestion in vitro. She concluded that in tryptic digestion the liberation of ammonia is due to an enzymic activity, whereas in peptic digestion it is due only to the acidity. The greatest activity was reached after from five to seven days.

*Bacterial Fermentation and Putrefaction.*—The common bacteria found in the intestine have been thoroughly investigated by Smith.<sup>10</sup>

6. Kantor, J. L., and Marks, J. A.: A Study of Intestinal Flatulence, *Ann. Int. Med.* **3**:403, 1929.

7. von Bunge, G.: *Lehrbuch der Physiologie des Menschen*, ed. 2, Leipzig, F. C. W. Vogel, 1905.

8. Schierbeck, N. P.: Ueber Kohlensäure im Ventrikel, *Skandinav. Arch. f. Physiol.* **3**:437, 1892.

9. Kraus-Ragins, L.: Rate of Ammonia Liberation in Tryptic and Peptic Digestion of Casein, *Proc. Soc. Exper. Biol. & Med.* **30**:452, 1933.

10. Smith, V.: Bacterial Flora of Isolated Intestinal Segments, *J. Infect. Dis.* **48**:204, 1921.



Closed intestinal loops in the dog, at different levels and with a variation in  $p_H$ , were studied. According to this author the most predominant bacteria encountered were *Clostridium Welchii* (87.5 per cent of the cases), *Bacillus coli* (85 per cent of the cases), *Streptococcus* (45 per cent of the cases) and *Staphylococcus* (32.5) per cent of the cases). Contrary to the common belief that *Cl. Welchii* does not thrive in alkaline mediums, an alteration in the flora was not noticed with a variation in the  $p_H$  from 5.8 to 8.89. No significant difference in the flora of the intestinal loops was observed at different levels.

Meleney, Berg and Jobling<sup>11</sup> studied bacteriologically the intestinal contents of dogs in which chronic duodenal obstruction had been produced. They concluded that normally *Cl. Welchii* was present in 70 per cent of the cases, varieties of the nonhemolytic streptococcus group in 50 per cent, and *B. coli* in 40 per cent. After obstruction the number of organisms was enormously increased, the increase being greatest in the *B. coli* group. Paine and Wilder<sup>12</sup> showed that a marked increase in the number of organisms occurred for a few days after obstruction but that there was a decided decrease as the obstruction progressed. They obtained intestinal fluid for counts by aspirating a segment of intestine that had been transplanted under the skin. Torrey<sup>13</sup> was able to isolate only a few organisms from material taken from above the ileum. *Cl. Welchii* and a few gram-positive diplococci were the only bacteria encountered. Organisms of the *B. coli* group first came in evidence in the ileum, and there also were found enormous numbers of the species *Cl. Welchii*. Torrey divided the intestinal bacteria into two groups, those which are fermentative and those which are putrefactive or, as in the case of *Cl. Welchii*, are found in a putrefactive flora although they are functionally fermentative. *B. coli* is intermediate between these two groups, according to Torrey, and possesses both fermentative and putrefactive properties. Kantor<sup>14</sup> expressed the belief that a certain quantity of gas is formed in the lower portion of the bowel by the fermentation of sugars and starches. The sugars and starches are broken down to monosaccharides by enzymic action. The monosaccharides that are not absorbed are available for decomposition to form carbon dioxide by bacterial action. Kantor further stated that carbon dioxide and fatty acids arise from cellulose when neutralized by the alkaline carbonates in the proximal portion of the

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11. Meleney, F. L.; Berg, B. N., and Jobling, J. W.: Chronic Duodenal Obstruction, *Arch. Surg.* **14**:762 (March) 1914.

12. Paine, J. R., and Wilder, L.: Personal communication to the author.

13. Torrey, J. C.: The Regulation of the Intestinal Flora of Dogs Through Diet, *J. M. Research* **39**:415 (Jan.) 1919.

14. Kantor, J. L.: A Study of Atmospheric Air in the Upper Digestive Tract, *Am. J. M. Sc.* **155**:829, 1919.

colon. He attributed this action on cellulose to a specific property of bacteria in the cecum. Schwartz<sup>15</sup> produced a large quantity of gas experimentally by decomposing cellulose at 38 C. One hundred grams of cellulose yielded 19.5 liters of carbon dioxide, 7.5 liters of methane and 4 liters of hydrogen. This showed the enormous amount of combustible gas as well as carbon dioxide which may result from this specific bacterial action on cellulose. Boycott and Damant,<sup>16</sup> working with goats on a diet of oats and hay, estimated by quantity of methane and hydrogen formed as being between 10 and 30 cc. per kilogram per hour. This is equivalent to from 3.5 to 6.6 per cent by volume of the total carbon dioxide produced in the same time. Boycott and Damant assumed that at least twice as much carbon dioxide as combustible gas arose from fermentation in the alimentary tract. Further, since the combustible gas is equal to 5 per cent of the total carbon dioxide, at least 10 per cent of the carbon dioxide formed arose from fermentation and not from tissue metabolism.

Not nearly so much gas originates from putrefaction of proteins as from fermentation of carbohydrates. The gas from putrefaction of proteins was said to form hydrogen sulfide and ammonia and was considered to be the only source of the latter gases.

*Diffusion of Blood Gases Into the Intestinal Lumen.*—McIver's<sup>17</sup> work on secretion of gas from the blood has attracted considerable attention. He found that when oxygen was injected into a closed loop of intestine there was not only absorption but a replacement of gas. The excreted gas consisted largely of nitrogen (from 20 to 30 per cent), with about from 5 to 6 per cent carbon dioxide. When carbon dioxide was injected it was absorbed rapidly and was not replaced. Nitrogen was absorbed slowly, and a small percentage of replacement by carbon dioxide and oxygen was observed. Kantor and Marks<sup>6</sup> explained the enormous displacement of nitrogen not only by the fact that it occurred under a partial pressure of about four-fifths atmosphere but also by the fact that the entire amount was held in a loose combination in the blood plasma. Ylppö,<sup>18</sup> in experiments on himself, found that after from forty to sixty minutes atmospheric air disappeared from the stomach. The remaining gas had a constant oxygen carbon

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15. Schwartz, E.: Ueber Flatulenz, *Med. Klin.* **5**:1339, 1909.

16. Boycott, A. E., and Damant, G. C. C.: A Note on the Quantities of Marsh Gas, Hydrogen and Carbon Dioxide Produced in the Alimentary Canal of Goats, *J. Physiol.* **36**:1837, 1907.

17. McIver, M. A.; Redfield, A. C., and Benedict, E. B.: Gaseous Exchange Between the Blood and the Lumen of the Stomach and Intestine, *Am. J. Physiol.* **76**:92, 1926.

18. Ylppö, A.: *Munchen med. Wchnschr.* **63**:1650, 1916.

dioxide ratio, which was similar to that of gas in the blood. He simultaneously analyzed alveolar air and demonstrated a constant ratio between the gases in the stomach and those in the blood. Dunn and Thompson<sup>19</sup> expressed the belief that all the carbon dioxide in the normal stomach, whether during fasting or after ingestion of food, could be accounted for by secretion or diffusion from the gastric mucosa. This is in contrast to the experiments of Schierbeck,<sup>8</sup> who showed that carbon dioxide was formed by chemical or bacterial action on foodstuffs. To prove this, Dunn and Thompson demonstrated that atmospheric air ingested or injected into the stomach tends to come into equilibrium with the gases in the blood within one hour in the case of carbon dioxide and much later, if at all, in the case of oxygen. The carbon dioxide content of the stomach during fasting was only 0.92 per cent less than that after ingestion of a full meal. In thirty-one of one hundred cases evidence of formation of gas was shown by only a few bubbles of gas when the gastric contents were incubated in a saccharimeter. Campbell<sup>20</sup> calculated the oxygen and carbon dioxide tensions in the mucous membranes by ascertaining the various concentrations of the gases above and below the normal limits. He found the normal oxygen tension in the stomach to be from 10 to 20 mm. of mercury, while the carbon dioxide tension was from 40 to 60 mm. of mercury. In the small intestine the tensions for oxygen and carbon dioxide were from 20 to 40 and from 35 to 60 mm. of mercury, respectively. Schoen<sup>21</sup> showed that after free carbon dioxide was injected into intestinal loops the average percentage of carbon dioxide increased to 6.2, or a tension of 47.1 mm. of mercury, in a short time.

*Passage of Atmospheric Air from the Stomach into the Intestine.*—Kantor<sup>14</sup> stated that the gas in the stomach consists of 80 per cent nitrogen and 20 per cent oxygen. Of this, oxygen is absorbed in part. Nitrogen, as demonstrated by McIver<sup>22</sup> and Schoen,<sup>21</sup> is extremely resistant to absorption and hence must either be belched up or pass through the entire gastro-intestinal tract. McIver,<sup>22</sup> directly observing the intestines of cats after distention of the stomach, noticed that the small intestine became distended as the stomach decreased in size. When the small intestine was obstructed, gas was seen to collect in the intestine above the obstruction. He attributed this not to diffusion from the

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19. Dunn, A. D., and Thompson, W.: The Carbon Dioxide and Oxygen Content of Stomach Gas in Normal Persons, *Arch. Int. Med.* **31**:1 (Jan.) 1923.

20. Campbell, J. A.: Gas Tensions in the Mucous Membranes of the Stomach and Small Intestine, *Quart. J. Exper. Physiol.* **22**:159, 1932.

21. Schoen, R.: Experimentelle Untersuchungen über Meteorismen, *Deutsches Arch. f. klin. Med.* **147**:224 (May) 1925; **148**:86 (July) 1925.

22. McIver, M. A.; Benedict, E. B., and Cline, J. W.: Postoperative Gaseous Distention of the Intestine, *Arch. Surg.* **13**:588 (Oct.) 1926.

blood but to passage of the gases from the upper portion of the gastro-intestinal tract down to a level proximal to the point of obstruction.

*Absorption of Gases.*—On this subject McIver's<sup>17</sup> work seemed to be outstanding. In experiments on cats he calculated the absorptive powers of the gases commonly found in the gastro-intestinal tract. He expressed the relative rates of absorption, in cubic centimeters, in a 25 cm. loop of small intestine over a period of one hour. They are as follows: carbon dioxide, 160; hydrogen sulfide, 69; oxygen, 17; hydrogen, 7.5; methane, 5, and nitrogen, 1.25. After injecting atmospheric air into the lumen of the intestine, he observed that the volume diminished during the first and second hours owing to the absorption of oxygen. After the oxygen tension had reached a level with the tension of the surrounding tissue, only 4 cc. disappeared in five hours.

The results reported in Schoen's<sup>21</sup> paper appear to be conclusive. Two hours after injecting pure oxygen into a closed intestinal loop he found that the gas consisted of 72 per cent of oxygen, 5 per cent of carbon dioxide and 22 per cent of nitrogen. When carbon dioxide was injected the volume of gas was 0 in experiments lasting from five to thirty minutes. Schoen introduced air containing 88.5 per cent of nitrogen, 11.5 per cent of oxygen and no carbon dioxide. One hundred and twenty minutes after the injection he found the gas to be composed of 83.8 per cent of nitrogen, 9 per cent of oxygen and 7.2 per cent of carbon dioxide. He wished to emphasize the fact that little nitrogen was absorbed and that the change was due more to the increase in carbon dioxide than to a decrease in nitrogen. The rate of absorption per minute as calculated by Schoen was from 0.135 to 0.2 cc. under a pressure of 7 cm. of water and from 0.2 to 0.3 cc. under a pressure of 2 cm. of water. Calculated per cubic centimeter of surface per minute, it was from 0.014 to 0.016. Hydrogen was found to have approximately the same rate of absorption as nitrogen. Schoen proved definitely that the important factor in retardation of absorption was the occurrence of dilatation and relaxation of the intestinal wall.

*Circulatory Interference.*—McIver<sup>22</sup> studied the absorbability of gases after partial occlusion of the portal veins. In two experiments in which he injected outside air, the volume increased after one or two hours. The increase in volume was due to the accumulation of carbon dioxide. The oxygen content decreased markedly. When carbon dioxide was injected into a loop, the volume decreased to more than one-half in ten minutes. The results of Schoen's<sup>21</sup> work were similar, but they indicated that no clinical condition, with the exception of mesenteric vascular occlusion, would simulate this experimental procedure. In

previous work I<sup>23</sup> demonstrated by means of roentgenograms that very little gas was observed after ligation of the veins alone but that after ligation of the arteries or of the arteries and the veins large quantities could be seen on the roentgenograms.

*Excretion of Gas by Way of the Blood and Lungs.*—Zuntz and Tacke<sup>24</sup> demonstrated that under normal conditions the combustible group of gases is eliminated mainly by way of the blood stream, only a small portion being expelled. In one experiment the total amount of gas excreted by rectum was 30 cc. in seven hours; of this 3 cc. was combustible gas. This is in contrast to the large amount excreted through the blood and lungs, namely, 100 cc.

#### METHOD OF ANALYSIS OF GAS

The gases of the obstructed intestine were analyzed by means of the apparatus used by the United States Bureau of Mines.<sup>25</sup> The carbon dioxide content was determined by absorption in 30 per cent potassium hydroxide; the oxygen content, by absorption in alkaline pyrogallol, and the hydrogen sulfide, by absorption in arsenous chloride. The volatile basic group was absorbed in a known acid and titrated with a known alkali. The hydrogen and the saturated hydrocarbon content were determined by the explosive method. In the experiments with animals samples of gas were drawn over mercury into specially made gas tubes while the animals were under ether anesthesia. The intestine was ligated over the tip of the inlet tube, after mercury had been forced to the top. By lowering the leveling bottle so as to produce a gentle suction and at the same time stripping the intestine toward the inlet tube the entire volume of gas was drawn into the gas tube. With this procedure the dead space was practically negligible, since control analysis checked satisfactorily. In the clinical cases in which operation was performed the gas was drawn over mercury directly from the intestine into sample tubes. Since in the cases in which no operation was performed decompression was brought about by continuous duodenal suction, the sample tube was connected directly to the rubber tubing leading to the suction apparatus by a three way stopcock. In order to prevent contamination from the air in the rubber tubing, the mercury was forced up to the stopcock, and as soon as gas was being obtained by the suction apparatus, it was shunted into the gas tube.

*Simple Obstruction of the Small Bowel.*—The origin and composition of gases which developed in cases of obstruction of the small bowel at a low level were investigated by four types of experiments.

In group A, simple mechanical obstruction was produced in thirteen dogs by dividing the intestine at the ileocecal junction and inverting the ends. Before the operation the animals received a general diet containing carbohydrates, proteins

23. Hibbard, J. S.; Swenson, P. C., and Levine, A. G.: Roentgenology of Experimental Mesenteric Vascular Occlusion, Arch. Surg. 26:20 (Jan.) 1933.

24. Zuntz and Tacke: Vortag über die Ursachen des Meteorismus, Deutsche med. Wchnschr. 10:717, 1884.

25. Burrell, G. A., and Seibert, F. M.: Sampling and Examination of Mine Gases and Natural Gas, Bulletin 197, U. S. Dept. Commerce, Bureau of Mines, 1926, p. 41.

and fats. They were offered food after operation, but they took both food and water sparingly. At intervals of from two days to three weeks they were anesthetized with ether, and the intestinal gas was drawn off for analysis. In addition, the total volume of gas and intestinal fluid was determined.

**Closed Loop Obstruction of the Small Bowel:** In group B different types of closed intestinal loops were studied, as this was considered the most applicable way in which swallowed atmospheric air could be excluded. The first series of experiments was confined to segments of intestine 2 feet (60 cm.) in length involving the jejunum or ileum. The animals were killed forty-eight hours after operation. The gas and fluid contents from the closed loops were aspirated and measured. A quantitative analysis could not be made because the amount of gas was too small. In a considerable number of animals in this series the tension caused by diffusion of fluid into the lumen of the bowel became so great that the formation of gas was probably considerably influenced. Many of the animals died of peritonitis as a result of perforation of the loops. In the second series, intestinal loops from 50 to 70 inches (127 to 178 cm.) in length were successfully produced by dividing the operative procedure into two stages.

**Simple Obstruction of the Small Bowel with Esophagostomy:** In the third series of experiments swallowed air was excluded by a different type of procedure. An esophagostomy, with closure of the distal end, was performed on animals in this series, either at the time the lower portion of the ileum was obstructed or a few days before. The gas present in the stomach was carefully aspirated in all experiments in which both procedures were accomplished in one stage. This type of experiment entirely excluded the undesirability of having a closed intestinal loop yet prohibited the gas formed within the bowel from being contaminated by atmospheric air.

**Closed Loops Receiving the Biliary and Pancreatic Secretions:** Owing to the emphasis which Kantor, Maury<sup>26</sup> and Bunting and Jones<sup>27</sup> have placed on the part played by the biliary and pancreatic secretions in both forming gas and in causing death, a third group (group C) of experiments was performed. This group consisted of experiments on animals in which long intestinal loops were made, into which the aforementioned secretions entered. In order to accomplish this a two stage operative procedure was used.

**Closed Loops Receiving Different Foodstuffs:** Many writers are of the opinion that the gas produced in the normal gastro-intestinal tract has been produced by the decomposition of foodstuffs. On account of this belief, various food substances, including carbohydrates, proteins and cellulose, which had passed through the stomach and small intestine of a normal dog were collected from an ileostomy and injected into the intestinal loops. The quantity used was determined by stripping the small bowel of a dog that had eaten a normal meal two hours previously.

In group B, series 1 (experiment with short intestinal loops), the animals' diet was limited to protein, carbohydrate or cellulose for a few days before the operation.

*Obstruction of the Large Bowel.*—The character of the gas occurring in association with obstruction of the large bowel was studied in experiments of similar

26. Maury, J. W. D.: Is Death in High Intestinal Obstruction Due to Absorption of Bile? *Ann. Surg.* **46**:556, 1907.

27. Bunting, C. H., and Jones, A. P.: Intestinal Obstruction in Rabbits, *J. Exper. Med.* **17**:192, 1913; **18**:25, 1913.

type. In Group D, series 1, the intestine was divided at the lowermost portion of the sigmoid flexure, and in series 2 an esophagostomy was performed in addition to the obstruction of the bowel so as to exclude atmospheric air.

### RESULTS AND COMMENT

The results of experiments and the observations in clinical cases are given in the tables.

*Quantitative Composition of Gas Occurring in Association with Obstruction of the Small Bowel.*—The results given in table 1 (group A) indicate that the composition of gases found in association with mechanical obstruction of the small bowel is different in some respects from that of gases occurring in association with other condi-

TABLE 1.—Group A: Simple Ileal Obstruction

Animal	Weight, Pounds	Duration of Experiment, Days	Fluid Content of Bowel, Cc.	Gaseous Content of Bowel							Volatile Basic Group, Per-centage
				Amount, Cc.	Carbon Dioxide, Per-centage	Oxygen, Per-centage	Nitrogen, Per-centage	Methane, Per-centage	Hydrogen, Per-centage	Hydrogen Sulfide, Per-centage	
1	55	2	150	100	...	...	...	...	...	...	...
3	50	2	...	...	4.7	10.00	65+	0	0	4.3	+
5	42	3	300	150	6.2	1.48	71+	0	0	7.86	+
7	48	3	290	200	12.7	1.10	60+	0	0	14.00	+
8	42	3	150	220	12.0	0.69	70+	0	0	2.00	+
9	46	3	220	290	9.3	1.00	74+	0	0	0.90	+
11	44	3	215	320	9.1	0.5	70+	0	0	4.30	+
22	55	3	1,198	325	13.1	1.8	73.6	0	0	9.40	2.0
35	36	5	400	200	11.5	0.9	79.4	0	0	6.50	1.5
34	34	7	200	300	8.8	2.00	66+	0	0	13.80	8.7
13	48	3	210	225	24.2	0.30	53.0	0	0.35	18.00	4.2
36	32	6	750	250	...	...	...	...	...	...	...
12	43	3*	420	430	15.0	1.50	23.0	0	0.5	45.10	+
Average.....			373	234							

\* The animal died three days after the operation.

tions reported in the literature. The presence of hydrogen sulfide and volatile basic gases was uniform throughout, and these gases appeared in large quantities in a considerable number of the cases. In all the experiments hydrogen sulfide occurred in the intestinal loop; its quantity varied from 1 to 18 per cent according to the duration of the experiment (table 1). In the more severe cases of obstruction there was noticed a gradual increase in hydrogen sulfide (from 14 to 18 per cent), and a marked rise (from 40 to 50 per cent) was observed after death of the experimental animal. Likewise, the volatile basic group was not absent in any of the analyses. Its concentration varied from 1 to 14 per cent, was found to be greater after the forty-eight and seventy-two hour periods and showed increase after death.

The results obtained with the combustible group (hydrogen and methane) of gases in cases of obstruction of the small bowel were entirely unexpected. Methane was present in only a few experimental animals and then in only a small amount (0.3 to 0.13 per cent). Simi-

larly hydrogen was absent except in three instances, occurring in low concentration (0.35 per cent) in one animal and in two cases in which the experimental animals had died four and six hours previously.

The average percentage of carbon dioxide in this group of experiments agrees with the results of previous experimental work on intestinal gases and shows a decided approach to that found in the blood. Apparently this is due to its high rate of diffusion and absorbability, as pointed out by McIver<sup>17</sup> and Schoen.<sup>21</sup> There is an indication that a rise in the carbon dioxide content occurs as the severity of the obstruction increases, but this fact needs further observation for verification.

The quantity of oxygen was from 10 to 12 per cent in the early hours of obstruction, but after the seventy-two hour period its value fell to a uniformly low figure.

The nitrogen content was consistently high throughout (from 60 to 90 per cent). This observation agrees with the literature in practically all the analyses of intestinal gas formed either normally or abnormally.

An explanation for the behavior of hydrogen sulfide, the combustible group and the volatile basic group of gases is extremely difficult. Fries<sup>28</sup> and Basch<sup>29</sup> have reported the presence of hydrogen sulfide in analyses in which the samples of gas were obtained by rectum. Hydrogen sulfide was not detected in samples of gas obtained directly from the stomach or small bowel in cases reported by Woodyatt and Graham,<sup>30</sup> Kantor and Marks,<sup>6</sup> McIver<sup>22</sup> and Basch.<sup>29</sup> The presence of gases of the volatile basic group has not been previously reported. Boycott and Damant<sup>10</sup> found large quantities of methane in the stomach of goats after the animals had received a food rich in cellulose. McIver<sup>22</sup> reported that small quantities of combustible gases were found in cases of paralytic ileus, but, as is generally the case, the samples were obtained by rectum. Undoubtedly, the greater part of the formation of methane and hydrogen is confined to the colon, as Kantor pointed out, and consequently those gases are not in evidence in cases of obstruction of the small bowel.

*Origin of Hydrogen Sulfide and Ammonia.*—It is generally conceded that the large amount of hydrogen sulfide and ammonia is entirely dependent on putrefaction of protein. Mathews<sup>31</sup> and MacLeod<sup>32</sup>

28. Fries, J. A.: Intestinal Gases of Man, *Am. J. Physiol.* **16**:468, 1906.

29. Basch, Seymour: *The Stomach and Intestinal Gases*, New York M. J. **88**:684, 1908.

30. Woodyatt, R. T., and Graham, E. A.: Secretion of Carbon Dioxide by the Alimentary Mucosa and Its Relation to Eructations of Gas and Abnormal Inflation of the Stomach and Intestine, *Tr. Chicago Path. Soc.* **8**:353, 1912.

31. Mathews, A. P.: *Text Book of Physiological Chemistry*, New York, William Wood & Company, 1925.

32. MacLeod, J. J. R.: *Physiology and Biochemistry in Modern Medicine*, St. Louis, C. V. Mosby Company, 1927.



pointed out that in the course of digestion and absorption of proteins free ammonia was split from the proteins. Some of these gases arose from the amide linkings during digestion as a result of the putrefactive action of bacteria in the intestine. Still another part was formed from the partial deamination of the amino-acids during the process of absorption. In addition, Mathews<sup>32</sup> emphasized that a large amount of ammonia occurred in the pancreatic secretions as well as in the gastric and intestinal mucosa. The quantity found in 100 Gm. of fresh intestinal mucosa was estimated to be from 23 to 48.9 mg. The quantity present in the normal intestinal mucosa as reported by Mathews amounted to about 40 mg. per hundred grams of fluid. Undoubtedly, some of the ammonia formed in the obstructed intestine is present in a complex combination as the amide ( $\text{NH}_2$ ), but nevertheless a large amount (from 0.5 to 3 per cent) of the fluid content occurs in simple inorganic combination, as has been shown by my analysis of the fluid contents of the obstructed bowel. This could probably be derived in part from an endogenous source and is free for volatilization, thus presenting an additional means by which ammonia may be formed.

According to Mathews,<sup>31</sup> the amount of sulfur entering the body as inorganic sulfate is approximately 0.6 Gm. per day. The remainder, which amounts to approximately 0.2 Gm., is organically bound. The ingested protein-bound sulfur is, for the most part, immediately utilized in the body. Mathews<sup>31</sup> showed that after a diet with reduced protein content the amount of neutral sulfur ( $\text{SO}_3$ ), instead of decreasing, rose markedly. In accordance with this observation, the neutral sulfur, instead of being derived from ingested protein, is probably largely derived from endogenous wear and tear. This could account for another source of hydrogen sulfide in the obstructed bowel.

Additional confirmation for the endogenous origin of the hydrogen sulfide and ammonia is presented by an analysis of the gas formed in a loop of intestine in which a pure culture of *Cl. Welchii* and 30 Gm. of dextrose were inserted. The amount of gas produced in ten hours was enormous, in fact so great that gas bubbles were observed penetrating the intestinal wall and extending into the mesentery and peritoneal cavity. The composition of the gas was found to be 13.5 per cent carbon dioxide, 2.24 per cent oxygen, 64.14 per cent nitrogen, 4.26 per cent ammonia and 15.9 per cent hydrogen sulfide. Certainly this experiment does not parallel conditions found in clinical cases of intestinal obstruction. Nevertheless, the same type of bacterial action is present in both, and although it is not nearly so fulminating in the clinical cases, the ultimate quality of the gases produced is quite significant.

*Source of the Gaseous Distention.*—It is difficult to determine accurately the quantity of gas originating either from the atmospheric air or from the body. Certain indications as to the routes of origin can be deducted by studying the results of experimental open and closed loop obstruction. From a comparison of the results in table 1 (group A) with those in tables 3, 4 and 5 (group B, series 2, 3 and 4), it is evident that the quantity of gas formed in the closed loops is much less than the average amount occurring in the open loops of comparable length. The gas observed in the closed loops either arises from the decomposition of the food or is derived from the blood and surrounding tissues. In consideration of the established fact that free nitrogen cannot form from digested food material, as shown by Krogh,<sup>33</sup> and of the observation that the gas formed in the loops consisted of 70 per cent nitro-

TABLE 2.—Group B, Series 1: Experiments with Closed Short Intestinal Loops

Animal	Weight, Pounds	Duration of Experiment, Hours	Diet	Fluid Content of Loop, Cc.	Gaseous Content of Loop, Cc.	Level of Loop
103	24	36	Normal	75	0	Jejunum
164	36	36	Normal	92	30	Jejunum
178	20	36	Normal	30	5	Ileum
154	44	36	Normal	42	20	Ileum
160	32	36	Normal	40	5	Ileum
123	18	36	Dextrose	90	15	Jejunum
122	21	36	Dextrose	248	7	Jejunum
144	26	36	Dextrose	115	8	Jejunum
115	34	36	Dextrose	45	10	Ileum
158	30	36	Dextrose	46	5	Ileum
130	31	36	Cellulose	28	12	Ileum
132	25	36	Cellulose	50	5	Ileum
131	27	36	Cellulose	114	11	Ileum
116	26	36	Cellulose	15	15	Ileum
118	32	36	Cellulose	2	8	Ileum
119	23	36	Cellulose	25	20	Ileum
114	20	36	Cellulose	15	25	Ileum

gen, it is obvious that the larger part of the gas present must have arisen by diffusion from the blood stream. This does not signify that the decomposition of foodstuffs produced gas amounting to only 30 per cent of the gas found in the closed intestinal loops; it indicates rather that this amount is present as the result of the obstruction. Certainly a much larger quantity is formed, but through rapid absorption and displacement of nitrogen it disappears readily. Probably, formation of gas from food material primarily produces a gaseous medium which is necessary for diffusion of gases from the blood into the intestinal lumen. The relative composition of the various gases is similar, with few exceptions, in these two types of obstruction. This is easily understood since the same processes of diffusion and absorption occur in each.

*Influence of Food on Character of Gas.*—The results given in tables 2 and 3 (group B, series 1 and 2) are contrary to those of other investigations on intestinal gases. They suggest that the composition of

33. Krogh, A. Standin, cited by McIver, Benedict and Cline.<sup>22</sup>

the gas was not greatly affected by the type of food ingested before operation or the type of digestive mixture injected into the loops. Not only was the relative percentage of gases unaltered, but the quantity produced did not show a marked variation. Probably if the experiments had been of short duration, or if a certain food element had been continuously injected into the bowel during the experiments, a marked variation in the composition of the gas would have resulted.

TABLE 3.—Group B, Series 2: Closed Loop Obstruction of Small Intestine

Animal	Weight, Pounds	Duration of Experiment, Days	Fluid Content of Loop, Ce.	Gaseous Content of Loop							
				Amount, Ce.	Carbon Dioxide, Per-centage	Oxygen, Per-centage	Nitrogen, Per-centage	Me-thane, Per-centage	Hydro-gen, Per-centage	Hydro-gen Sulfide, Per-centage	Volatile Basic Group, Per-centage
2	36	2	60	90.0	....	....	....	..	..	.....	....
4	42	2	150	70.0	4.50	12.3	87.0	..	..	.....	....
19	40	3	225	83.0	8.20	2.30	74.6	0	0	12.78	1.62
38	42	3	1,050	40.0	10.00	4.00	+	..	..	3.00	+
28	30	5	130	10.0	....	....	....	..	..	.....	....
40	44	8	200	100.0	....	....	....	..	..	.....	....
31	38	3*	600	40.0	5.12	2.8	50+	0	0	15.36	+
14	46	3*	...	....	18.00	1.10	11+	0.13	3.2	62.74	+
17	52	3*	...	....	13.00	1.75	37+	0	2.33	42.20	+
27	26	4*	350	20.0	....	....	....	..	..	.....	....
Average			136	65.5							

\* The animal died.

TABLE 4.—Group B, Series 3: Simple Ileal Obstruction with Esophagostomy

Animal	Weight, Pounds	Duration of Experiment, Hours	Fluid Content of Bowel, Ce.	Gaseous Content of Bowel					
				Amount, Ce.	Carbon Dioxide, Per-centage	Oxygen, Per-centage	Nitro-gen, Per-centage	Me-thane, Per-centage	Hydro-gen Sulfide, Per-centage
78	36	72	250	110	12.8	1.1	76.3	0	0.0
79	34	72	240	140	9.0	3.2	85.0	0	0.0
89	41	72	300	40	9.5	0.4	73.4	0	8.2

*Influence of Bile and Pancreatic Juice on Character of Gas.*—In experiments of group C, in which the intestinal loop received the biliary and pancreatic secretions, the results were not so satisfactory. Death occurred in all experimental animals within sixty hours after operation, and it was impossible to obtain samples of gas for analysis before death. Although the small quantity of gas formed as a result of this type of procedure stands out quite strikingly, the composition of the gas cannot be reliably interpreted. At the most, it can only signify that the composition of gas occurring after death is not greatly different from that present after death in cases of the other types of obstruction.

*Quantitative Composition of Gas in Association with Obstruction of the Large Bowel.*—From observation of the composition of the gases occurring in the experiments on obstruction of the large bowel (tables 6 and 7), it is evident that the values for nitrogen and carbon dioxide compare favorably with the concentrations occurring in association with obstruction of the small intestine. The percentage of nitrogen appeared to be high, and the carbon dioxide content, with a few exceptions, was close to that in venous blood. The oxygen content dropped to an extremely low value. This agrees with the figures reported by McIver.<sup>22</sup>

Hydrogen and methane were found to be present in all the samples, although their concentration was uniformly low. This is in contrast

TABLE 5.—Group B, Series 4: Simple Ileal Obstruction with Esophagostomy\*

Animal	Weight, Pounds	Duration of Experiment, Hours	Fluid Content of Bowel, Cc.	Gaseous Content						Hydrogen Sulfide, Per-centage
				Amount, Cc.	Carbon Dioxide, Per-centage	Oxygen, Per-centage	Nitrogen, Per-centage	Methane, Per-centage	Hydrogen, Per-centage	
50	43	72	250	100	12.0	5.7	76.2	0.0	0.0	6.1
59	28	72	225	100	...	...	...	...	...	...
55	45	72	100	60	12.8	0.9	71.6	0.3	0.4	14.4

\* The animals received no food before operation.

TABLE 6.—Group C, Series 1: Obstruction of the Sigmoid Flexure

Animal	Weight, Pounds	Duration of Experiment, Hours	Fluid Content of Bowel, Cc.	Gaseous Content						Hydrogen Sulfide, Per-centage
				Amount, Cc.	Carbon Dioxide, Per-centage	Oxygen, Per-centage	Nitrogen, Per-centage	Methane, Per-centage	Hydrogen, Per-centage	
77	50	192	650	285	6.5	1.2	80.0	2.6	0	6.7
82	47	72	100	215	10.8	1.4	80.6	1.6	0	5.6
81	59	72	110	375	13.0	0.8	80.1	1.0	1	3.1

to the absence of these gases in association with obstruction of the small bowel. 1. The fact that the values for the combustible gases were much less than the concentration occurring in the flatus of normal persons can probably be explained by the marked dilution and relatively high rate of absorption of those gases.

The percentage of hydrogen sulfide was similar to the concentration found in the previous experiments.

*Source of the Gaseous Distention Associated with Obstruction of the Large Bowel.*—A comparison of the quantity of gas formed in association with open obstructions of the large bowel with that observed after closed obstruction (tables 6 and 7) leads one to believe that a large part of the gas occurring in association with obstruction of the large bowel is endogenous. The distention is not due only to diffusion of

gas into the intestine and to decomposition of contents of the large bowel; the excess gas must also be derived from the contents of the small bowel passing into the colon.

### CLINICAL STUDY

In addition to the experiments on animals described, a number of clinical cases demonstrating various types of ileus were available for study.

*Distention of the Small Bowel.*—Comparison of the character of the gas occurring in the three cases of distention of the small bowel

TABLE 7.—Group C, Series 2: Obstruction of the Sigmoid Flexure with Esophagostomy

Animal	Weight, Pounds	Duration of Experiment, Hours	Fluid Content of Bowel, Cc.	Gaseous Content						
				Amount, Cc.	Carbon Dioxide, Percentage	Oxygen, Percentage	Nitrogen, Percentage	Methane, Percentage	Hydrogen, Percentage	Hydrogen Sulfide, Percentage
83	44	72	150	165	10.0	1.4	63.2	+	12.4	10.1
86	40	72	125	450	18.4	0.5	53.8	0.6	4.2	12.6
90	30	72	220	310	12.2	1.4	73.4	2.8	1.6	8.6

TABLE 8.—Group D: Closed Loop Obstruction with Biliary and Pancreatic Secretions

Animal	Weight, Pounds	Duration of Experiment, Days	Fluid Content of Loop, Cc.	Gaseous Content of Loop							
				Amount, Cc.	Carbon Dioxide, Per-centage	Oxygen, Per-centage	Nitrogen, Per-centage	Methane, Per-centage	Hydrogen, Per-centage	Hydrogen Sulfide, Per-centage	Volatile Basic Group, Per-centage
26	36	1.50*	326	75	13.7	0.35	28.4	0.3	0	43.7	13
29	38	0.75*	670	25	....	....	....	..	..	....	..
30	44	2.00*	600	0	....	....	....	..	..	....	..
37	40	2.50*	750	0	....	....	....	..	..	....	..

\* The animal died.

with that found in the dogs with simple low obstruction of the bowel shows that there was a marked similarity. The concentration of nitrogen was uniformly high; the carbon dioxide content approached that found in the blood, and the oxygen concentration was low (except in case 5). Gases belonging to the combustible group were entirely absent both in the experiments on animals and in the clinical cases, a fact which further supports the statement of Kantor and Marks<sup>6</sup> that those gases are formed by a specific bacterial action in the colon. The concentration of hydrogen sulfide and of gases of the volatile basic group appeared to be high and approached the concentration found in dogs with far advanced stages of obstruction.

*Distention of the Small and Large Bowel.*—Samples of gas were obtained in four cases of generalized peritonitis associated with marked degrees of distention of the small and large bowel. In case 9 the gas was collected directly from the small intestine one and one-half hours after death. In the remaining cases samples were obtained by suction applied to an inlying duodenal tube. The high concentration of oxygen occurring in case 10 probably indicated that the gas was aspirated from the stomach instead of from the duodenum. The high concentration of oxygen in gas from the stomach has been previously mentioned by Kantor<sup>14</sup> and Dunn and Thompson.<sup>15</sup> The results show that the concentration of nitrogen and carbon dioxide agrees closely with the concentration occurring in the previous studies. The oxygen content, although higher than expected, probably represents an accurate figure

TABLE 9.—*Clinical Cases of Distention of the Small Bowel*

Case	Diagnosis	Roentgen Findings	Method of Obtaining Gas	Composition of Gas						
				Nitro-gen, %	Oxy-gen, %	Car-bon Di-oxide, %	Hydro-gen, %	Me-thane, %	Hydro-gen Sulfide, %	Vola-tile Basic Group, %
1	Mechanical obstruction of ileum	Marked distention of small bowel	Aspiration at operation	60	3.0	9.4	0	0	14.0	13.6
5	Mechanical obstruction* of ileum	Marked distention of small bowel	Suction with nasal catheter	70	10.0	9.0	0	0	5.8	5.2
3	Mechanical obstruction	Distention of small bowel	Aspiration at operation	79	2.9	8.1	0	0	10.0	...

\* In this case the disorder proved to be spastic ileus at operation four months later.

for gas occurring in the upper portion of the intestinal tract. Small amounts of hydrogen and methane were present in all cases, which signifies that a diffusion of gases from the small and large bowel occurred through an open ileocecal sphincter. Their low concentration suggests either that fermentation is less active than in normal persons, as stated by McIver,<sup>22</sup> or that the cases are diluted by a marked diffusion of gases from the blood into the lumen of the bowel. Considering the large quantity of gas present, the latter theory is more probable. The percentage of hydrogen sulfide present indicates a moderate degree of putrefaction and approaches the concentration observed in dogs with early stages of obstruction.

*Obstruction of the Large Bowel.*—Four cases of obstruction of the large bowel were studied. In two of the cases samples of gas were obtained by suction of the duodenum by means of nasal catheters, and in the other two, directly from the large bowel. Since an analysis of

the gas obtained in the first two cases showed that it was free from hydrogen and methane, it can be concluded that the distention was confined almost entirely to the large bowel. Roentgenographic reports in the two cases bear out this conclusion. The competency of the iliocecal valve, as previously mentioned by Wangensteen,<sup>21</sup> apparently accounts for the exclusion of gas from the colon from the upper portion of the intestinal tract.

McIver<sup>22</sup> analyzed the gas, collected by rectum, occurring in a series of cases of postoperative ileus and found that the percentage of hydrogen and methane was much less than that occurring in a group of medical cases in which no operation was performed. He concluded that a large amount of the gas originated from swallowed air, because it resembled atmospheric air so closely.

TABLE 10.—*Clinical Cases of Paralytic Ileus*

Case	Diagnosis	Roentgen Findings	Method of Obtaining Gas	Composition of Gas					
				Nitrogen, Per-centage	Oxygen, Per-centage	Carbon Dioxide, Per-centage	Hydrogen, Per-centage	Methane, Per-centage	Hydrogen Sulfide, Per-centage
9	Diffuse peritonitis	Distention of small and large bowel	Aspiration for 1½ hours post mortem	74.2	0.2	7.7	1.2	+	7.7
15	Diffuse peritonitis	Distention of small and large bowel	Suction with nasal catheter	71.6	4.4	10.6	6.6	+	6.2
11	Diffuse peritonitis	Distention of small and large bowel	Suction with nasal catheter	64.6	8.0	11.8	6.3	1.0	8.4
14	Diffuse peritonitis	Distention of small and large bowel	Suction with nasal catheter	80.4	10.0	5.6	0.3	0.0	3.7

In the two cases (cases 2 and 20) in which samples of gas were obtained directly from the colon the gas contained small amounts of hydrogen and methane, in contrast to the large amount occurring in flatus, the percentage for the various gases being as follows: nitrogen, 51.4; oxygen, 9.6; carbon dioxide, 16.5; hydrogen, 8.1; methane, 14.4, and hydrogen sulfide, +3. Undoubtedly, the marked dilution by the gases from the blood, the displacement of nitrogen and the fast rate of absorption of these two gases explain these results.

*Increase in Hydrogen Sulfide After Death.*—It has previously been shown in this paper that the percentage of hydrogen sulfide not only appeared to be definitely increased during the terminal stages of obstruction but mounted to an extremely high concentration after death. A partial explanation for these findings can be deduced from a study of the  $p_H$  of the fluid contents of the dilated bowel. Determinations

were made on a group of animals with terminal ileal obstruction soon after the obstruction was produced and repeated during the terminal stages, and on a similar group of dogs many hours after death. In contrast to the acid reaction of normal intestinal contents as described by McClendon and Shedlov,<sup>34</sup> Karpman and Thompson, Grayzel and Miller,<sup>35</sup> Graham and Emery<sup>36</sup> and Ling and Fenger, the contents of the obstructed intestine were found to be alkaline in all experiments. It is evident from table 12 that the alkalinity of the intestinal contents increased in proportion to the duration of the obstruction until it reached its maximum peak, a  $p_H$  of about 8, just before death occurred. After death the  $p_H$  decreased rapidly to the acid side (table 13). Since the saturation of hydrogen sulfide in the fluid contents was greatest at the high  $p_H$  occurring just before death, a large volume of hydrogen sulfide

TABLE 11.—*Clinical Cases of Obstruction of the Large Bowel*

Case	Diagnosis	Roentgen Findings	Method of Obtaining Gas	Composition of Gas					Hydrogen Sulfide, Per-centage
				Nitro-gen, Per-centage	Oxy-gen, Per-centage	Carbon Dioxide, Per-centage	Hydro-gen, Per-centage	Me-thane, Per-centage	
8	Carcinoma of rectum	Distention of large bowel	Suction with nasal catheter	76.4	17.0	3.4	0.8	0.0	2.8
6	Carcinoma of splenic flexure	Distention of large bowel	Suction with nasal catheter	77.2	13.2	7.2	0.0	0.0	2.4
20	Carcinoma of rectum	Distention of large bowel	Aspiration of colostomy loop	74.0	1.2	8.4	4.0	2.6	10.2
2	Carcinoma of rectum	Distention of large bowel	Aspiration of colostomy loop	69.0	3.4	11.0	8.0	1.0	7.2

would be liberated after death, as a result of the sudden drop in  $p_H$ . The rise in the concentration of hydrogen sulfide during the terminal stages of obstruction can be explained only by an increased putrefaction of proteins, combined possibly with a decrease in the absorption of the gas.

*Analysis of Gases of the Volatile Basic Group.*—Although it was impossible to subdivide further the gases designated as the volatile basic

34. McClendon, J. F.; Shedlov, A., and Thompson, W.: The Hydrogen Ion Concentration of the Ileum Content, *J. Biol. Chem.* **31**:269, 1917. McClendon, J. F.; Shedlov, A., and Karpman, B.: The Hydrogen Ion Concentration of the Contents of the Small Intestine, *ibid.* **34**:1, 1918.

35. Grayzel, David M., and Miller, Edgar G., Jr.:  $p_H$  Concentration of Intestinal Contents of Dogs with Special Reference to Inorganic Metabolism, *Proc. Soc. Exper. Biol. & Med.* **24**:668, 1927.

36. Graham, W. R., and Emery, E. S.: The Reaction of the Intestinal Contents of Dogs Fed on Different Diets, *J. Lab. & Clin. Med.* **13**:1097, 1928.



group, added information was obtained by separating the volatile bases in the fluid contents, since they were, in all probability, the direct precursors of this group of gases. The total amount of volatile bases of the fluid was determined by titration, and the ammonia was separated quantitatively by permittit and nesslerized. Qualitative tests were made on the ammonia-free portion for primary, secondary and tertiary amines by the method described by Hinsberg.<sup>37</sup> The results showed that the percentage of ammonia consistently amounted to about one half of the volatile basic group. The remaining half gave positive qualitative reactions for primary and tertiary, but negative reactions for secondary, amines.

TABLE 12.—*Determination of Hydrogen Ion Concentration of Fluid Contents After Obstruction of the Small Bowel*

Animal	Type of Obstruction	First Determination			Second Determination		
		Duration of Experiment, Days	pH	Condition of Animal	Duration of Experiment, Days	pH	Condition of Animal
40	Long closed loop	8	7.65	Fair	11	8.26	Died in 12 hours
39	Simple low ileal obstruction	4	7.55	Fair	9	7.95	Weak, staggering
41	Simple low ileal obstruction	2	7.60	Fair	6	7.57	Fistula developed on 5th day; recovery
42	Simple low ileal obstruction	2	7.38	Good	4	7.67	Internal perforation; death on 6th day

#### TOXICITY OF GASES

Carbon dioxide, oxygen, nitrogen, hydrogen and methane in the quantities in which they occur in association with intestinal obstruction are generally considered to be nontoxic.

The dangers of hydrogen sulfide poisoning, by inhalation, has been stressed by Yant.<sup>38</sup> He stated that an atmosphere containing 0.1 per cent hydrogen sulfide may cause almost immediate cessation of respiration, followed by death. During the early experiences with large amounts of hydrogen sulfide in the petroleum industry many deaths from acute poisoning were reported. However, in the gastro-intestinal tract the gas rarely occurs in amounts significant enough to cause toxic symptoms. According to McIver,<sup>17</sup> a marked fall in blood pressure may

37. Hinsberg, in Sidgwick, N. V.: *Organic Chemistry of Nitrogen*. London, Clarendon Press, 1910.

38. Yant, W. P.: *Hydrogen Sulphide in Industry: Occurrence, Effects and Treatment*, Am. J. Pub. Health 20:598, 1930. Yant, W. P., and Fowler, H. C.: *Hydrogen Sulphide Poisoning in the Texas Panhandle, Big Lake, Texas*, McCamey, Texas Oil Fields, U. S. Bureau of Mines Reports of Investigations, serial 2776, 1926, p. 20.

be expected a few minutes after injection of as little as 20 cc. of the pure gas into loops of the small intestine. This toxic effect is apparently confined to concentrations much higher than those occurring in cases of obstruction. In experiment 50, in which a 20 per cent concentration of hydrogen sulfide was used, no toxic symptoms were observed. Analysis of the gas twenty-four hours later revealed an almost complete absorption of the hydrogen sulfide.

Since the fluid contents of the bowel must be saturated before hydrogen sulfide is liberated, an added source of danger exists in the absorption of the solution of hydrogen sulfide. Accordingly, a series of three experiments were made in which from 600 to 800 cc. of a saturated

TABLE 13.—*Postmortem Determination of Hydrogen Ion Concentration Fluid Contents After Obstruction of the Small Bowel*

Animal	Type of Obstruction	$p_{\text{H}}$	Number of Hours Between Death and Determination
31	Long closed loop.....	6.8	24
37	Long closed loop.....	6.7	4
40	Long closed loop.....	6.7	12
60	Simple low ileal.....	6.3	30
62	Simple low ileal.....	6.2	24

TABLE 14.—*Toxicity of Gases Injected into a Long Intestinal Loop*

Animal	Gas Injected Into Loop	Amount, Ce.	Results of Analysis of Gas Twenty-Four Hours Later						
			Nitrogen, Per-centage	Oxygen, Per-centage	Carbon Dioxide, Per-centage	Hydrogen, Per-centage	Methane, Per-centage	Hydrogen Sulfide, Per-centage	Ammonia, Per-centage
50	20% hydrogen sulfide in room air	300	87.0	6.8	2.59	0	0	1.83	1.78
51	20% ammonia in room air	300	89.7	1.6	4.58	0	0	4.12	0

solution of hydrogen sulfide was injected into intestinal loops. In experiment 53 the  $p_{\text{H}}$  of the fluid was elevated to 9 in order to increase the solubility of the hydrogen sulfide. The experimental animals showed no symptoms of toxicity, and at autopsy, twenty-four hours later, the fluid was found to have been absorbed.

Likewise extremely toxic effects of ammonia have been reported to follow inhalation of a sufficiently concentrated amount. Apparently the small quantities formed within the lumen of the bowel can be absorbed and detoxicated. In experiment 54 symptoms of toxicity were not observed when a 20 per cent concentration of ammonia was injected into a closed intestinal loop. The complete disappearance of the gas twenty-four hours later must be accounted for by its marked solubility in the fluid contents of the bowel and its rapid absorption.

# SIXTIETH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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## CONGENITAL DEFORMITIES

*Congenital Flatfoot.*—Congenital flatfoot gives a varied clinical and roentgenologic picture according to Krukenberg.<sup>1</sup> A deforming prenatal force pushes the forepart of the foot upward. This produces a certain amount of bowing of the bones of the foot and brings the whole foot into valgus and calcaneus. Treatment consists of correcting the calcaneus with a plaster cast. This treatment is continued for about seven months. Treatment applied early gives the best functional results. Operative correction may be required in older children. Diagnosis is made by the clinical picture of persistent valgus and calcaneus and by roentgenograms which show a vertical axis for the astragalus and a crossing of this axis with the axis of the os calcis. Associated congenital deformities are common.

*Congenital Supination Deformity of the Forefoot.*—Hohmann<sup>2</sup> describes a supination deformity of the forefoot observed at birth, normal relations existing in the posterior part of the foot. It may be

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This report of progress is compiled from a review of 228 papers selected from 269 titles relating to orthopedic surgery and appearing in medical literature approximately between Oct. 15, 1935, and March 1, 1936. Only those which suggested progress were chosen for review.

1. Krukenberg, H.: Ztschr. f. orthop. Chir. **62**:385, 1935.

2. Hohmann, G.: Ztschr. f. orthop. Chir. **63**:263, 1935.

unilateral or bilateral. He considers it to be a contracture at the distal tarsal joints due to the position in utero. Treatment consists of fixation in valgus and plantar flexion with a plaster cast. Manual manipulations are helpful after the cast is removed.

[ED. NOTE.—These congenital deformities of the feet are not uncommon. They usually respond quickly to treatment; at times spontaneous correction occurs.]

*Treatment of Congenital Clubfoot.*—Brown<sup>3</sup> suggests an ingenious method of correcting clubfoot in infants and young children. An aluminum foot piece is applied to the deformed foot, from the outer side of which traction is made to pull the foot in eversion and dorsiflexion by running an elastic band from the foot piece to a strip of adhesive tape on the outer side of the thigh. When the child begins to walk a similar aluminum foot piece is incorporated in the sole of the shoe. In the case of older children a bivalved plaster cast is also worn at night.

*Results of Treatment of Congenital Dislocation of the Hip.*—Gaugele and Kienzle<sup>4</sup> report on 190 children with congenital dislocation of the hip treated between 1920 and 1925 who were examined in 1933 and 1934 clinically and roentgenologically. The importance of the earliest possible reduction, gentleness and fixation in the modified Lorenz position for from eight to ten months is emphasized. With the first cast the abduction is from 30 to 40 degrees, and with the second it is from 70 to 80 degrees; both casts are in external rotation and are left on for a total of from fourteen to sixteen weeks. An abduction brace designed by Gaugele is worn for from eight to ten months. Good functional results were obtained in 171 children (90 per cent), who became able to walk normally. Anatomic results were as follows: One patient had complete redislocation; 11 children showed subluxation; deformities of the acetabulum, described as "lemon-shaped," were noticed, being mild in 25 and severe in 4 patients; coxa vara was observed in 3 children; deformities of the head of the femur occurred in 15 children. In the authors' opinion, 85.76 per cent of the patients showed roentgen evidence of satisfactory healing. They are conscious that these figures are far more satisfactory than the pessimistic figures reported in other series and believe that the results in their more recent cases are even more promising.

[ED. NOTE.—Children with congenital dislocation of the hip should be followed for from twenty to twenty-five years before end-results can be determined. Both functional and anatomic changes take place throughout the entire period of growth.]

3. Brown, L. T.: J. Bone & Joint Surg. **18**:173, 1936.

4. Gaugele and Kienzle: Deutsche Ztschr. f. Chir. **245**:214, 1935.

*Late Results of Treatment of Congenital Dislocation of the Hip.*—Heyman<sup>5</sup> examined 50 children who had a reduction of a congenital dislocation of the hip five or more years before. Functionally the results were considered good in 30 cases and fair in 8; in 12 they were regarded as failures. Of the patients showing good functional results, 25 had unilateral dislocations. A study of the roentgenograms of the hips showed practically normal osseous structure in 10 children; in 10 there were moderate changes; 30 showed marked changes in the head of the femur and the acetabulum, and 1 child showed coxa vara. Heyman believes that the developmental changes in the acetabulum and the head of the femur in cases of congenital dislocation are not identical with those in cases of Legg-Perthes' disease.

#### OSTEOMYELITIS

*Acute and Chronic Osteomyelitis in the Child.*—Allende<sup>6</sup> in a well written monograph reviews the various theories of the location of osteomyelitis in the metaphyses in children. He expresses the belief that trauma produces a temporary vasoconstriction and in this way favors the local growth of bacteria. He discusses the conservative, expectant and operative treatment. In very young children the draining of a subperiosteal abscess may be all that is required. Often a period of rest and general upbuilding for from one to three days is advisable before operation. Early opening into the infected site favors the spread of the infection rather than helps healing. Trephining is a procedure of election which if done improperly or prematurely may double the mortality and complications. Subperiosteal section and diaphysectomy are rarely indicated. Osseous resection should be performed only after from fifteen to twenty days of drainage. The method of Orr has been used by Allende in his clinic at Cordoba, Spain, almost exclusively in cases of chronic osteomyelitis. Immobilization should be continued until sufficient osseous regeneration has occurred to permit function; this requires from seven to twelve months. Sequestrectomy should be carried out when sequestrums are well demarcated, the acute stage of the disease is past and the general condition is good. Obliteration of osseous cavities after sequestrectomy, by muscle suture or muscular flaps if possible, is advised. Articular complications were one of the most frequent difficulties in Allende's series, occurring 25 times in 129 patients. For the simple effusion into the joint Allende advises immobilization; in cases of purulent effusion arthrotomy is necessary, and

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5. Heyman, C. H.: Late Results of Treatment of Congenital Dislocation of the Hip, J. A. M. A. **106**:11 (Jan. 4) 1936.

6. Allende, G.: Asociacion Argentina de Cirugia, Septimo Congreso Anual, Buenos Aires, 1935.

ankylosis is a frequent outcome. He states that fracture has been observed frequently in the femur and in the humerus, but he does not give the number of instances in which this occurred. When fracture occurs adequate drainage, packing with petrolatum gauze and immobilization should be resorted to. Secondary osseous localizations, a frequent complication, are usually benign; they often heal spontaneously, and only rarely can organisms be grown from such lesions. In the general treatment serotherapy, transfusions and ultraviolet irradiation are helpful. Vaccine therapy has not been established as yet on a practical basis. A summary of 129 cases and a thorough review of the literature are given.

*Chronic Osteomyelitis Associated with Malignant Changes.*—Henderson and Swart<sup>7</sup> reported 5 cases of malignant changes in sinuses of patients with chronic osteomyelitis. They refer to Benedict's<sup>8</sup> article, published in 1931, in which are reported 12 cases of malignant degeneration among 2,400 cases of osteomyelitis. Henderson and Swart state that Benedict, like earlier authors, recognized two types of tumors: the superficial type, which is easily recognized, and the deep type. They urge that even though malignant degeneration is rare, all sinus tracts be cleaned if possible, that if one tract has a foul odor and bleeds easily malignant degeneration be suspected and that if such degeneration is proved by biopsy amputation be performed. High voltage roentgen therapy should follow amputation.

#### POLIOMYELITIS

Wilson and Walker<sup>9</sup> describe unusual features in the epidemic of poliomyelitis which occurred in California in 1934. There were 3,333 cases with 110 deaths. More than 57 per cent of the patients were over 10 years of age, while 27 per cent were over 20. Among these older patients an atypical form of the disease was frequently observed, in which sensory, vasomotor and arthritic symptoms predominated. These often consisted of recurrent exacerbations of acute disturbances.

#### SYPHILIS

*Infantile Congenital Syphilis with Positive Roentgen but Negative Serologic Findings.*—Ingraham<sup>10</sup> found that the Wassermann reaction was of value in diagnosing syphilis in only 9 cases among 195 offspring

7. Henderson, M. S., and Swart, H. A.: J. Bone & Joint Surg. **18**:56, 1936.

8. Benedict, E. B.: Surg., Gynec. & Obst. **53**:1, 1931.

9. Wilson, J. C., and Walker, P. J.: Acute Anterior Poliomyelitis: Orthopedic Aspects of the California Epidemic of 1934, Arch. Int. Med. **57**:477 (March) 1936.

10. Ingraham, N. R., Jr.: Roentgen-Positive Seronegative Infantile Congenital Syphilis, Am. J. Dis. Child. **50**:1444 (Dec.) 1935.

of syphilitic mothers. Roentgenographic examination discovered the condition in 40 additional cases. Of these 49 cases, in 26 the disease was recognized before the patient was 6 days of age, and in 23, when the patient was between the ages of 1 and 10 months. In all these cases the initial skeletal changes were evident roentgenologically before the Wassermann reaction of the blood became positive. In 3 cases, serial roentgenograms of the same child taken over a period of several months showed the gradual progression of the pathologic changes. The Wassermann reaction, which was originally negative, became positive as the disease progressed.

#### TUBERCULOSIS

*Tuberculosis of the Symphysis Pubis.*—Pytel<sup>11</sup> reports a case of proved tuberculosis of the symphysis pubis in a child aged 10 years and reviews the literature. He finds that the symphysis pubis is less commonly affected by tuberculosis than any other joint in the body. Because of the inconstancy of symptoms diagnosis is difficult. Often the first sign is a swelling close to the symphysis or in the perineum. This sometimes simulates a hernia. The most common symptom is frequency of micturition. Whether conservative or radical treatment is used, the prognosis is good unless the disease is complicated by pregnancy. Eleven cases in pregnant women have been reported in which rupture of the symphysis pubis occurred during delivery, the outcome being fatal in all but 1 case.

[ED. NOTE.—In the experience of several of us one of the earliest symptoms of tuberculosis of the symphysis pubis has been pain in one or in both sacro-iliac joints. We believe that it occurs more frequently than this article suggests.]

*Tuberculosis of the Shafts of Long Bones.*—Petter and Medelman<sup>12</sup> report 9 cases and give roentgenograms showing tuberculous changes in the shafts of long bones. They believe the condition to be rare. This series represents 2.9 per cent of all the cases of tuberculosis of the bones and joints observed by them. They conclude that the condition is primarily destructive in the cancellous portion of the long bones but that when it approaches the periosteum it becomes proliferative.

#### CHRONIC ARTHRITIS

*Studies Relating Vitamin C Deficiency to Rheumatic Fever and Rheumatoid Arthritis.*—Rinehart<sup>13</sup> lists the changes which occur in experimental animals as scurvy develops from a diet deficient in vita-

11. Pytel, A.: Rev. d'orthop. **22**:348, 1935.

12. Petter, C. K., and Medelman, J. P.: Am. Rev. Tuberc. **32**:285, 1935.

13. Rinehart, J. F.: Ann. Int. Med. **9**:671, 1935.

min C. He also describes carefully the pathologic manifestations of subacute or chronic scurvy, which include: (1) synovial proliferation and formation of pannus in the joints of the animals, (2) subsynovial and peritendinous deposits of fibrin and connective tissue cells, (3) thinning and retrogression of the articular cartilages, (4) rarefaction of bone, (5) atrophy of muscle and (6) formation of subcutaneous nodules. He states that these changes occur in the absence of infection but that when infection is superimposed on the chronic scurvy the pathologic process is accentuated. The fundamental similarities of these experimental lesions to those of rheumatoid arthritis are pointed out. Rinehart reports 4 cases of so-called rheumatoid arthritis in which careful inquiring into the dietary habits of the patients revealed faulty diets particularly low in foods containing vitamin C. These patients showed low levels when tested for capillary resistance (test for latent scurvy). When they were given diets high in vitamin C the level of capillary resistance was raised; symptoms in the joints were diminished, and the general condition was improved.

*Experimental and Pathologic Studies in the Degenerative Type of Arthritis.*—Bauer and Bennett<sup>14</sup> suggest the use of the term degenerative arthritis for the type of chronic arthritis referred to as arthritis deformans, osteo-arthritis, hypertrophic arthritis or senile arthritis. They conclude that the changes found in joints of elderly persons and in joints which have been artificially traumatized are similar and are primarily degenerative. The microscopic and macroscopic changes are described. Since the changes are primarily degenerative and are due to excessive use and wear and tear of the surfaces of joints, Bauer and Bennett see little value in the removal of foci, the use of an elaborate diet, endocrine therapy, etc. They suggest that loss of weight, if indicated, correction of mechanics and insurance that anklyosis of the joints will not follow are the chief measures of therapy. They admit that there may be factors present to produce changes more rapidly in some persons than in others, but they state that no evidence has been produced to warrant such a conclusion.

*A Roentgenologic Study of Acromial Arthritis.*—Lindblom<sup>15</sup> studied roentgenograms of the shoulders of 419 patients. Roentgenograms were made with the patient in the supine position, with the arm abducted and externally rotated. A second picture was made with the hand under the neck. These views gave pictures of the acromioclavicular joint. Two hundred and fourteen patients complained of pain and limitation of motion in the shoulder. In 68 this first appeared after an injury. The

14. Bauer, W., and Bennett, G. A.: J. Bone & Joint Surg. **18**:1, 1936.

15. Lindblom, K.: Acta chir. Scandinav. **77**:175, 1935.



changes found were: (1) formation of tiny or moderately large subchondral defects or massive productive changes about the margin of the joint in persons over 60; (2) narrowing of the joint space; (3) partial or complete destruction of the joint space. Lindblom found calcifying peritendinitis, subacromial bursitis, a rarer disease than acromioclavicular arthritis. He believes that this type of arthritis frequently plays a part in producing pain about the shoulder.

#### THE BACK

*The Intervertebral Disk.*—Joplin<sup>16</sup> discusses the embryology, anatomy, physiology and pathology of the intervertebral disk and reviews the changes which take place in this disk in infancy, childhood, adult life and old age. The significance of thin disks and that of thickened disks are discussed, and the pathologic changes which take place in rupture of the intervertebral disks are described, as are degenerative changes which occur under the stress and strain of daily activity. The article gives a good review of one phase of a clinical entity which is becoming better known.

*Changes in Development in the Vertebral Articular Facets.*—Kuhns<sup>17</sup> made a study of 500 roentgenograms of the spine of children and examined portions of the dorsal part of the spine removed as a routine at 50 autopsies. He found that the vertebral articular facets were evident roentgenologically between the ages of 6 months and 2 years but that their articular margins were not clear before the age of 8 years. Deformities of the vertebral articular facets which occurred in congenital anomalies, diseases and injuries involving the vertebra could best be demonstrated by roentgenograms taken in slightly oblique positions. The usual deformities were: (1) disalignment of the articulating surfaces, (2) proliferative changes and (3) ankylosis. Such conditions hindered correction of spinal deformity, produced osteoarthritis and led to irritation of the roots of spinal nerves.

#### NEOPLASMS

*An Analysis of Living Patients with Primary Malignant Tumor of Bones.*—To 86 cases of verified malignant tumor of bones accepted as instances of five year cure by the Sarcoma Registry of the American College of Surgeons, Campbell<sup>18</sup> adds 14 more cases of "cure" from his own files, bringing the total to 100 cases. In 10 of Campbell's 14 cases the tumor was an osteogenic sarcoma of some type; in 4 it was

16. Joplin, R. J.: Surg., Gynec. & Obst. **61**:591, 1935.

17. Kuhns, J. G.: Radiology **25**:498, 1935.

18. Campbell, W. C.: An Analysis of Living Patients with Primary Malignant Bone Tumors, J. A. M. A. **105**:1496 (Nov. 9) 1935.

an endothelial myeloma (Ewing's tumor). These cases were collected from a series of 125 instances of malignant tumor of the bones in patients treated by Campbell. He noticed that the osteoblastic and osteolytic tumors of children were practically always fatal. The chances of "cure" of both osteogenic and nonosteogenic tumors increased with increasing age. The results of biopsy seemed to make little difference in the prognosis. Campbell advocates amputation above the affected bone.

*Osseous Metastases with Carcinoma of the Stomach.*—Kerr and Berger<sup>19</sup> collected all the reports of cases (143) of osseous metastasis in patients with carcinoma of the stomach and added 5 cases to the series. They observed that metastasis to bone was most frequent at the sites of the red marrow, spine, ribs, femur, sternum and pelvis. Metastases might be osteoplastic, osteoclastic or both without regard to the primary lesion; in fact, the site, size and type of a primary tumor had nothing to do with the appearance of osseous involvement. Bony metastases were observed to occur at any age but were more frequent in the young.

*Hemangioma of Voluntary Muscle.*—MacDermott<sup>20</sup> reports 2 cases of hemangioma of voluntary muscles. While these tumors have been known to occur in a great variety of situations, the majority are found in the quadriceps, gastrocnemius, triceps and masseter muscles. The most common age incidence is between 11 and 25 years.

*Traumatic Hemangiomatous Tumors of Skeletal Muscle.*—A mixed capillary and arterial angioma, arising in a skeletal muscle following definite trauma, is described by Mailer,<sup>21</sup> who advances an explanation of how such tumors may arise and why they may show infiltrating characters. Of the 256 cases of angioma of muscles mentioned, trauma was cited as a possible cause in 17 per cent.

#### THE FOOT

*March Foot Associated with Undescribed Changes in the Internal Cuneiform and Metatarsal Bones.*—Maseritz<sup>22</sup> reviews extensively the literature on the subject and reports 1 case in which there were fragmentation of the internal cuneiform bone, fracture of the head of the second metatarsal bone and fracture of the base of the fifth metatarsal bone. He believes that in this condition there is an underlying disturbance of the calcium content of the bone.

19. Kerr, H. D., and Berger, R. A.: Am. J. Cancer **25**:518, 1935.

20. MacDermott, E. N.: Brit. J. Surg. **23**:252, 1935.

21. Mailer, R.: Brit. J. Surg. **23**:245, 1935.

22. Maseritz, I. N.: Surg., Gynec. & Obst. **61**:818, 1935.

## NEUROMUSCULAR DISTURBANCES

*Volkmann's Ischemic Paralysis.*—It is impossible to do justice in a short review to this excellent article of over 100 pages by Massart<sup>23</sup> which presents, with the possible exception of the chapter on elective ionization, a clear and detailed exposition of Volkmann's paralysis. The main points brought out by Massart may be briefly stated as follows: Electrical reactions showed that the median nerve is most constantly and most severely affected. The ulnar nerve is sometimes affected but not as severely. Massart believes that the deformity is due more to nerve degeneration than to muscle degeneration. He reviews experimental facts, emphasizing the work of Jepson, Brooks and Nario, particularly that of Nario, who produced Volkmann's contracture by artificially sclerosing the end-arteries. Massart states that the distribution of the nerves and vessels in the forearm is not constant, according to dissection of specimens and to arteriography on living subjects. The important factor is the presence of nonelastic fascial compartments, which allows pressure to accumulate. The treatment to be used depends on the stage at which the paralysis is first seen. According to Massart surgical treatment may be: 1. Immediate. This consists in incising the fascia over the flexor muscles. 2. Delayed. This may be resorted to after several weeks have elapsed and the fracture has healed. If the artery is intact, periarterial sympathectomy is advised; if the artery has been severed or is occluded, a resection should be performed instead. 3. Late. Under this heading are operations done after the pathologic process has produced definite sequelae. He considers the operations under the following headings: 1. Operations on the bones. If shortening of the bones is decided on it should be performed at the wrist rather than in the forearm. 2. Operations on the tendons. These operative procedures proved to be of doubtful value. 3. Operations on the muscles. Transplantation of the origin of the flexor muscles Massart regards as permissible, but he stated that at the same time the cicatrized portions of the muscle bellies should be excised. He also states that treatment by apparatus is valuable but should not be used to the exclusion of the surgical and physical therapeutic measures.

## ROENTGENOLOGY AND ROENTGENOLOGIC TECHNIC

*Roentgenograms on a Curved Cassette to Show Loose Bodies in the Knee Joint.*—By means of a curved cassette placed under the knee, which was flexed 45 degrees, the tube being placed at a right angle to the tibia, Béclère<sup>24</sup> took pictures which showed the intercondylar notch and the joint space to be greatly enlarged. A slight amount of distortion

23. Massart, R.: *Rev. d'orthop.* **22**:386, 1935.

24. Béclère, H.: *Presse méd.* **43**:1839, 1935.

was apparently present, but this accentuated any loose bodies present. Judging from the reproductions published, this method offers a valuable means of locating foreign bodies in the knee joint.

#### THE KNEE

*Injuries to the Semilunar Cartilages.*—Pannett<sup>25</sup> does not consider that it is possible to remove the whole of the semilunar cartilage through an anterior incision, and he is of the opinion that a posterior incision should be used also if a total extirpation is required or if trouble in the posterior end of the semilunar cartilage is suspected. He does not consider that it is necessary to remove the whole cartilage if there is merely a typical "bucket handle" tear or a pedicled fragment, as removal of these separated portions may be carried out successfully without touching the remaining part of the cartilage, provided that it is firmly attached. He considers that the absence of "locking," combined with sudden attacks of disability, casts suspicion on the integrity of the posterior end of the cartilage.

[ED. NOTE.—In the case of "bucket-handle" tears of the menisci we believe that it is important to remove both portions of the split cartilage.]

*The Innervation of the Skin of the Anterior Aspect of the Knee.*—Schmidt<sup>26</sup> found that in more than half of a group of 100 patients at the clinic in Königsberg, Germany, operations on the knee were followed by sensory disturbances in that region. He studied 16 knees of cadavers and observed that the variations in innervation emphasized by workers like Schangina exist. He reproduced a series of segmental variations. The sensory innervation of the anterior aspect of the knee arises from above and medially. The branches pass down and laterally. Almost regularly the joint line is crossed 3 cm. medial to the patellar tendon by a good-sized branch of the femoral cutaneous nerve or an infra-patellar branch of the saphenous nerve. In analyzing the various incisions designed to avoid branches of nerves, Schmidt remarks that there is no incision which is sure to avoid dividing some anterior sensory nerve, while it is true that a lateral incision wherever it can be used is far less likely to cause trouble. Diagrams of the sensory innervation of the knee are given.

#### CIRCULATORY DISTURBANCES OF THE EXTREMITIES

*Thrombophlebitis Migrans.*—Jaki<sup>27</sup> reports 2 cases of thrombophlebitis migrans in which extraction of definitely infected teeth terminated the disease. In each case the lesions were of long duration.

25. Pannett, C. A.: Brit. M. J. 2:439, 1935.

26. Schmidt, M. D.: Deutsche Ztschr. f. Chir. 245:411, 1935.

27. Jaki, J.: Zentralbl. f. Chir. 62:2056, 1935.

While various causes have been reported, Jaki believes that the disorder is due to sensitization of the various tissues to some obscure infectious focus. Excision of a segment of diseased cephalic vein substantiated the reported findings of Ceelen<sup>28</sup> that all coats of the vein wall are involved by the inflammatory process. The surrounding tissues are also inflamed. In the productive, obliterating tissue, nonspecific giant cells are to be seen.

#### MISCELLANEOUS

*Free Bodies in Joints.*—Pfab<sup>29</sup> reviews 72 cases of loose bodies in the joint cavities, 44 occurring in the joint of the knee, 23 in that of the elbow, 2 in that of the hip, 2 in that of the ankle and 1 in that of the shoulder. The causative factor in 31 cases was chondromatosis; in 29 it was osteochondritis dissecans, and in 12, trauma. In almost every case a severe trauma or repeated milder injuries were necessary for the development of symptoms. In cases of osteochondritis dissecans and chondromatosis Pfab believes that there is a constitutional tendency. In his series treatment was wholly surgical.

[ED. NOTE.—Chondromatosis in our experience is a much rarer condition than this paper indicates.]

*Dupuytren's Contracture of the Fingers.*—Niederland<sup>30</sup> maintains that while it may be true that inheritance predisposes to the development of this lesion, it is definitely recurrent trauma (usually industrial) that causes the contracture to develop in the palmar fascia. This is a matter of considerable importance in compensation insurance practice. He remarks incidentally that this was the view of Felix Plater, an anatomist of Basel, Switzerland, who, in 1614, long before Dupuytren, described the lesion and outlined its causation.

*Brittle Bones and Blue Scleras.*—McGregor<sup>31</sup> reports the case of a child with brittle bones and blue scleras whose father was similarly affected. Examination of the family tree showed that the condition was present in 15 members during three generations.

*Movements of the Wrist Joint.*—From a detailed roentgenologic examination of the wrist joint, Wright<sup>32</sup> concludes that radial deviation occurs entirely at the transverse carpal joint and that ulnar deviation is brought about almost wholly by a sliding movement of the radiocarpal joint. He considers that flexion and extension occur in the radiocarpal and transverse carpal joints, movement at the latter being more extensive.

28. Ceelen, W.: Zentralbl. f. Chir. **61**:1517, 1934.

29. Pfab, B.: Arch. f. orthop. u. Unfall-Chir. **35**:618, 1936.

30. Niederland, W.: Zentralbl. f. Chir. **62**:2238, 1935.

31. McGregor, H. M.: Guy's Hosp. Rep. **85**:356, 1935.

32. Wright, R. D.: J. Anat. **70**:137, 1935.

*Rusting of Tissues with Rustless Nails and Wires.*—Hoase<sup>33</sup> has observed in several patients injury to tissues from the action of rustless nails (nails that do not rust in water). He presents photomicrographs of tissue showing granulations with phagocytic cells containing iron. A photograph is given of a nail which showed extensive rusting after being in the neck of the femur for fourteen months. Similar changes are seen with rustless wire and Steinmann pins in six weeks. The nickel and chromium coating is lost through the action of tissue fluids. Changes in the metal can be seen as early as fourteen days after it becomes lodged in the tissues.

#### ORTHOPEDIC OPERATIONS

*Operative Treatment of Habitual Dislocation of the Patella.*—Kapel<sup>34</sup> reviews the treatment of permanent and recurring dislocations of the patella. Forty-four operations, 9 of which were bilateral, were performed on 35 patients. All except 2 of the patients had a lateral dislocation. Studies of the end-result were carried out in 4 cases of permanent dislocation. In 1 of these the dislocation had recurred. Operations for habitual dislocation of the patella were reviewed in 29 patients, of whom 6 had dislocation of the patella of varying degree. Kapel had used the method of Goldthwait and that of Krogus and the plastic repair method of Hübscher. He concluded that in permanent subluxation of the patella an osteotomy of the femur should be performed; the extensions of the quadriceps muscle should then be freed and the patellar ligament reattached.

*Stabilization of the Hip by Transplantation of the Anterior Muscles of the Thigh.*—Wagner and Rizzo<sup>35</sup> advocate transplantation of the upper attachment of the tensor fasciae latae, the sartorius and the straight head of the rectus femoris muscle in cases of paralysis of the gluteus medius muscle associated with weakness of the gluteus maximus. They believe that it not only gives more stability to the hip than other procedures but also adds to the stability of the knee. The operative technic is described and reports of cases are given.

*Stabilization of the Acromioclavicular Joint.*—Wakeley<sup>36</sup> reviews 5 cases of dislocation of the acromioclavicular joint in patients on whom he operated during the last twenty-one years. The operation consisted of exposing the area by an incision through the anterior fibers of the deltoid and encircling the joint with silver wire passed through two holes

33. Hoase, W.: Arch. f. orthop. u. Unfall-Chir. **35**:683, 1935.

34. Kapel, O.: Acta chir. Scandinav. **77**:201, 1935.

35. Wagner, L. C., and Rizzo, P. C.: J. Bone & Joint Surg. **18**:180, 1936.

36. Wakeley, C. P. G.: Lancet **2**:708, 1935.

drilled horizontally through the clavicle and the acromion parallel to the joint. The convalescence was short, and the end-results were satisfactory.

*The Radical Operation for Hallux Valgus.*—In studies on 28 patients who had undergone the Heuter-Mayo type of operation, Bughi<sup>37</sup> found that 9 were completely free from pain and satisfied with the results of operation, that 14 still had pain and that 5 were dissatisfied. He states that the 5 patients in the latter group were all of the asthenic type. Roentgenograms showed marked shortening of the first metatarsal bone.

*A New Amputation of the Lower Third of the Thigh.*—In an excellently illustrated article Callander<sup>38</sup> discusses amputation of the lower portion of the thigh and describes in detail the technic of his operation. The essential features of the operation are as follows: The anterior flap includes the soft tissues of the upper part of the leg as far as the level of the tibial tuberosity, while the posterior flap is a little longer and extends well down on the gastrocnemius muscle. The popliteal vessels and nerves are ligated through an amuscular and avascular cleavage plane on the medial aspect of the lower part of the thigh. All the hamstring muscles are severed at their tendinous insertions on the tibia, and the femur is sectioned in the condylar flare just proximal to the adduction tubercle. The patella is dissected from the anterior flap from the side of the joint, leaving the rectus femoris tendon in the floor of the patellar fossa to act as an end-bearing buffer for the femur. No coapting primary sutures are used throughout the operation save from four to six skin clips or sutures which hold the flaps roughly in position. As the edges of the flaps unite, the posterior flap retracts gradually but extensively until the femur occupies the patellar fossa snugly and the suture line is located well up behind the end of the stump. There was 1 death among 14 patients operated on by this method. Callander believes that operative mortality, shock, repairs and infections with gas bacilli are less likely to occur than when the classic methods are used.

#### FRACTURES AND DISLOCATIONS

*Local Anesthesia for Vertebral Fracture.*—Böhler<sup>39</sup> advises the use of a short needle for the injection of 10 cc. of a 1 per cent solution of procaine hydrochloride for anesthesia in the reduction of vertebral fractures. In the usual fracture produced by sharp flexion of the body

37. Bughi, I.: *Chirurg* 7:138, 1935.

38. Callander, C. L.: A New Amputation of the Lower Third of the Thigh, *J. A. M. A.* 105:1746 (Nov. 30) 1935.

39. Böhler, L.: *Chirurg* 7:562, 1935.

a compression of the anterior portion of the vertebra occurs and at the same time a tear of the posterior longitudinal ligament with or without a portion of the spinous process. A superficial hematoma develops over the longitudinal ligament. The procaine hydrochloride is injected into this hematoma, the needle being introduced from 5 to 6 cm. to the side of the midline.

*Avulsions of the Spinous Processes.*—Avulsions of the lower cervical or upper dorsal spinous processes occurring at work, Matthes<sup>40</sup> states, are best seen by means of roentgenograms taken in the semi-oblique position with the tube focused just past the scapula. Treatment consists of a double loop shoulder brace of leather. Like the old corset for treatment of round shoulders the brace draws the shoulders back. It is worn for ten days. Then treatments with hot air and active motion are instituted. Later massage is employed. The spot of tenderness is often present four weeks later. After eight weeks the average patient has no disability for labor. It is of importance to reassure the patient, who is usually impressed with the concept that his spine has been fractured. Fibrous union with excess local calcification usually occurs. Matthes believes that for residual pain operations are useless. In a ten month period he found fractures of the spinous processes in 82 workers, almost half of whom were under 30 years of age.

*Late Results of Dislocation of the Upper Extremity and Its Prevention.*—Wachsmuth and Kremer<sup>41</sup> studied the late results of this injury in 142 patients with dislocations in the upper extremity; 81 patients had dislocation of the shoulder, 36 of the elbow, 21 of the fingers and 2 of the wrist. In 2 there was a nerve injury, the insult being of the brachial plexus in 1 patient and of the axillary nerve in the other. There was evidence of osteo-arthritis in 53 per cent of the injured joints. Spurs were frequently seen in painless joints. In 1 of the elbows myositis ossificans developed; in 6 there were mild peri-articular osseous shadows. In 10 shoulders habitual dislocation occurred. Wachsmuth and Kremer urge early reduction and early motion.

*The Mechanism of Scapular Fracture.*—Takács<sup>42</sup> experimented on 68 scapulae in cadavers; 62 were fractured by the methods used. In the first experiment the scapula was struck posteriorly with a 2 Kg. hammer in imitation of a fall on the flat surface of the scapula. A blow on the body of the scapula produced a stellate fracture. With the cadaver lying in the prone position a blow on the acromion or spine produced a fracture of the coracoid process. When a weight was

40. Matthes, H. G.: *Chirurg* 7:666, 1935.

41. Wachsmuth, W., and Kremer, F. J.: *Chirurg* 7:41, 1935.

42. Takács, Z.: *Ztschr. f. orthop. Chir.* 62:354, 1935.



placed under the shoulder (with the cadaver in the prone position) a heavy blow on the acromion produced a fracture of the glenoid fossa. A blow struck on the elbow while the upper part of the arm was extended usually produced a fracture of the neck of the scapula. Takács concludes that direct fractures were those of the acromion and of the body, spine, lateral or medial edge or one part of the margin of the scapula. Indirect fractures were those of the coracoid process, the glenoid fossa and neck and other parts of the margin of the scapula.

*Nailing of Fractures of the Humeral Head.*—Vose<sup>43</sup> reports 4 operative fixations of fracture of the surgical neck of the humerus after conservative reduction had failed. By the use of the V-shaped incision of Bardenheuer (which outlines the deltoid insertion on the humerus), the deltoid is pulled back, exposing the humeral shaft. Instead of the Smith-Petersen nail Vose uses a large two-flanged nail. To insert it without splintering the shaft he saws a V-shaped oblique groove and enlarges it with the chisel. He states that early motion may be performed and that the end-results are good.

[ED. NOTE.—Roentgenograms showed epiphyseal perforation in 2 children. Excess bone formation appeared in another. The nail is large and difficult to insert, and its use appears to have no advantage over simpler methods employed for internal fixation in special cases.]

*Fracture of the Base of the Radius in Adults.*—Cornell<sup>44</sup> from a study of 155 cases of fracture of the lower end of the radius in 140 patients found that the incidence of major deformities of bone was as follows: (1) shortening of the radius averaging about  $\frac{1}{6}$  inch (0.4 cm.), in 78 per cent; (2) widening of the wrist joint, in 75 per cent; (3) tilting of the distal radial fragment posteriorly, in 76 per cent; tilting anteriorly, in 14 per cent; (4) comminution of the lower fragment, in 68 per cent; (5) fractures of the ulnar styloid process, in 72 per cent (in 60 per cent of these fractures nonunion occurred). In treatment molded plaster splints were used; in 55 cases the wrist was put up in acute flexion; in 90 cases it was put straight, and in 10 cases, in extension. The average period of immobilization was twenty-two days. Motion of the fingers was encouraged at the outset, and active motion of the wrist on the ninth or tenth day. General anesthesia induced by nitrous oxide and oxygen was used for reduction. End-results showed that of the 140 patients 100 returned to work in an average time of fourteen weeks.

43. Vose, O.: Beitr. z. klin. Chir. **162**:190, 1935.

44. Cornell, N. W.: Fracture of the Base of the Radius in Adults, Arch. Surg. **31**:897 (Dec.) 1935.

*Treatment of Colles' Fracture.*—Devenish<sup>45</sup> describes a method of maintaining a Colles fracture in reduction while an accurately fitting plaster splint is applied. The fracture is reduced with the patient under general anesthesia, and then the pronated forearm is placed on an inclined plane which terminates just short of the fracture line. A loop of 1½ inch (3.8 cm.) bandage is placed over the wrist and hangs down toward the floor. An assistant maintains light traction on the fingers, and the operator places a foot in the loop of bandage and maintains pressure while a posterior slab is applied to the forearm and hand; a circular bandage is applied to keep the splint in position. Accurate molding of the slab into the hollow produced by the tightness of the loop is considered to be an important point in the procedure.

*Fracture of the Carpal Scaphoid.*—Cravener<sup>46</sup> states that fractures which involve the scaphoid are more important from the standpoint of treatment than fractures of the tuberosity because of the frequency of nonunion. Roentgenograms should be made with the hand in the extended first position and in slight ulnar deviation in order that the surfaces of the fracture be kept parallel to the roentgen rays. The theories of nonunion are reviewed. Cravener advocates bone pegging as the method which so far, he states, has given perfect functional results. His technic consists of making a 2 inch (5 cm.) linear incision over the dorsum of the wrist and a transverse cut in the capsule. A drill is inserted in the scaphoid at the junction of the dorsal ligament, and a hole is made through both fragments. A roentgenogram is made to localize the drill, and an osteoperiosteal bone graft is driven into the hole. The wrist is put up finally in 45 degrees dorsiflexion and slight radial deviation for from six to eight weeks.

*A Survey of the Management of Intracapsular Fractures of the Neck of the Femur.*—Dickson<sup>47</sup> reviews the various methods of closed reduction in external fixation and gives the results from his clinic. The leg traction method of Roger Anderson Well was used in 15 cases with results as follows: bony union in 2 cases, nonunion in 11 and death in two. Dickson believes that the constant traction in this method tends to hold the fragments apart and minimizes interlocking. Treatment according to the method advised by Whitman resulted in bony union in 70 per cent of the 68 cases in which it was used, nonunion in 14.7 per cent and death in 13 per cent. In 9 cases the Smith-Petersen nail was used, the results being bony union in 7 cases and death in 2. The Albee (or Jones) bone graft operation for nonunion of intracapsular fracture was used in 4 cases, in all of which bony union resulted. The

45. Devenish, E. A.: *Lancet* 2:821, 1935.

46. Cravener, E. K.: *New York State J. Med.* 35:807, 1935.

47. Dickson, F. D.: *J. Missouri M. A.* 32:481, 1935.

reconstruction procedure of Whitman was used in 7 cases with excellent results in 5, failure in 1 and death in 1. In 4 cases the method of Brackett was employed, and satisfactory results were obtained in all. This excellent paper not only includes a review of the methods of treatment but gives results from some recognized clinic other than that of Dickson.

*Malunited Fractures Affecting the Ankle Joint.*—Kimberley<sup>48</sup> studied a series of 216 patients with fractures of the ankle from the New York Orthopaedic Dispensary and Hospital. Of this number 24 were subjected to ankle fusion because of malposition of fragments and persisting pain; of the 22 who were observed long enough to permit an estimation of the end-results, 20 were improved. Emphasis was placed on correction of any lateral displacement of the foot and on putting the foot in maximum dorsiflexion such that from 3 to 9 degrees of equinus remains. The technic of the operative procedure is described.

*Therapy for Fracture of the Os Calcis.*—Felsenreich,<sup>49</sup> from Böhler's clinic in Vienna, Austria, states that the three chief failures in treatment of fracture of the os calcis have been: (1) traumatic arthritis with marked atrophy of the bones and severe injury to the articulations. (2) contracted flatfoot with abduction and pronation from faulty muscular pull and (3) disorders resulting from too early and active resumption of weight bearing unsupported or too vigorous exercises. Standing and walking were usually resumed too early. In a review of 42 cases he stresses the points which he considers important for good recovery. He believes that errors occur chiefly in the care of the injury during convalescence. Simple fracture without displacement may be treated in plaster casts permitting walking, but careful supervision must be given to prevent displacement and excessive irritation to joints. More severe fractures (groups 5 to 8 of Böhler's classification) are usually reduced by wire fixation and counter skeletal traction on the os calcis as soon as the severe swelling has subsided. Traction is maintained for from six to ten weeks. After removal of the plaster cast active and resistive exercises are given in bed often for two or more weeks. The nonweight-bearing period is indefinitely prolonged when marked atrophy of the bone is present. By these means Felsenreich has prevented in almost all recent cases the three types of failure mentioned.

*Fracture of the Astragalus, an Injury of Persons Who Fly Gliders.*—Schneider<sup>50</sup> has observed 12 fractures of the astragalus in two years occurring in the landing of gliders (a type of airplanes). The frequency of such fractures has been for the greater part prevented by

48. Kimberley, A. G.: Surg., Gynec. & Obst. **62**:79, 1936.

49. Felsenreich, F.: Arch. f. orthop. u. Unfall-Chir. **35**:590, 1935.

50. Schneider, J.: Arch. f. orthop. u. Unfall-Chir. **35**:80, 1935.

adding foot plates to the steering bar so that pressure comes on the entire foot instead of on the long arch alone. Treatment of these injuries has consisted of traction with from 3 to 6 Kg. for from six to fifteen days. Then a snug-fitting plaster was applied. Weight bearing was often delayed for three months, and Schneider states that an elastic bandage may be worn for three months longer. He believes that these fractures heal much more slowly than the textbooks state. Of the 12 patients whom he observed, 1 had a completely stiff ankle (fracture with rotation); 1 underwent amputation of the foot; 1 had limitation of motion from bony spurs; the remaining 9 had good function.

*Ligaments of the Arch of the Foot and the Mechanism of Metatarsal Fractures.*—Bruno<sup>51</sup> stresses the importance of the plantar fascia in the mechanism of fractures of the metatarsal bones. Its divisions to the second and third metatarsal bones bear most of the weight of the body. The second and third metatarsal bones are supplied, therefore, with rigid fascial bands which permit least motion of these bones. Excess forces on these comparatively unyielding bows result in fracture. The second metatarsal bone, which is thinnest, fractures most frequently.

#### RESEARCH

*Anatomic Observations on the Development of Necrosis of the Carpal Semilunar Bone.*—Köstler<sup>52</sup> studied the blood supply of the carpal semilunar bone and found that the arteries are not end-arteries but have adequate anastomosis on the dorsal side. The joint capsule has a deep fold on the dorsal side. Through trauma such as may result from pressure—as in drilling—on the hand in dorsiflexion, this capsular fold may become thickened. Köstler believes that this can in certain cases cut off the blood supply to the semilunar bone.

*Blood Flow Through Skeletal Muscle in Relation to Its Contraction.*—From a large series of experiments carried out on the blood vessels of the gastrocnemius muscle in dogs, Anrep and von Saalfeld<sup>53</sup> showed that muscular contraction is accompanied by compression of the intramuscular blood vessels. They also demonstrated that the hyperemia in a muscle which normally follows contraction is greatly increased if the muscle is perfused with venous blood collected during the activity of the muscle. Perfusion of venous blood obtained when the muscle was at rest did not have this effect. It was presumed, therefore, that some active vasodilator substances are produced and released from the contracting muscles. These substances are stable in the blood for

51. Bruno, G.: *Chirurg* 7:209, 1935.

52. Köstler, J.: *Arch. f. orthop. u. Unfall-Chir.* 36:34, 1935.

53. Anrep, G. V., and von Saalfeld, E.: *J. Physiol.* 85:375, 1935.

at least half an hour. Their exact nature has not been determined, but Anrep and von Saalfeld are of the opinion that it is unlikely that acetylcholine plays any part in the production of the hyperemia.

*Effect of Large Doses of Roentgen Rays on the Growth of Young Bones.*—Regen and Wilkens<sup>54</sup> treated one extremity of each of 8 young rabbits with heavy doses of roentgen rays and studied the effect by roentgen observations on the growth of bone at stated intervals until adult life was reached. Six rabbits of the same age were used as controls. Regen and Wilkens found that there was an initial increase in growth during the first month, followed by a rapid diminution during the following eight months of the study.

*Influence of Roentgen Irradiation on the Rate of Healing of Fractures.*—Regen and Wilkens<sup>55</sup> also treated the bones of adult rabbits for two weeks and for one day, respectively, before producing the fracture. They found that there was marked delay in healing as well as diminution in phosphatase activity at the site of the fracture. The phosphatase activity gradually rose to normal after reaching a low level at the end of three weeks.

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54. Regen, E. M., and Wilkens, W. E.: J. Bone & Joint Surg. 18:61, 1936.

55. Regen, E. M., and Wilkens, W. E.: J. Bone & Joint Surg. 18:69, 1936.

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## EFFECT OF ACETYLCHOLINE AND OF PHYSOSTIGMINE ON GASTRO-INTESTINAL MOTILITY

OBSERVATIONS OF NORMAL ANIMALS AND OF ANIMALS WITH  
EXPERIMENTAL PERITONITIS

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The extensive literature on the treatment of paralytic ileus and the constantly increasing number of methods for inducing intestinal motility indicate the lack of a satisfactory therapy for intestinal atonia. Recent attention has been directed toward acetylcholine and its probable function as the chemical mediator of parasympathetic nerve impulses. As such, it has been considered as an agent initiating gastro-intestinal motility, and attempts have been made to treat both experimental and clinical paralytic ileus with this preparation. It has been shown, however, that acetylcholine has an extremely evanescent action and that it is rapidly destroyed in the body by a specific ferment (esterase) which splits the ester into acetic acid and relatively inactive choline.

Physostigmine salicylate in extremely high dilutions has been found to inhibit the action of the esterase and greatly to augment and prolong the action of acetylcholine. These facts have not been applied clinically in the use of acetylcholine to stimulate gastro-intestinal motility, and without them, the evaluation of the effect of acetylcholine is difficult. For this reason, we have studied the action of acetylcholine and of physostigmine in stimulating gastro-intestinal motility in normal dogs and in animals in which the production of experimental paralytic ileus has been attempted.

### REVIEW OF THE LITERATURE

Since Reid Hunt's<sup>1</sup> observations in 1906 of the vasodilator effects of choline esters, acetylcholine and its derivatives have received con-

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From the Laboratory of Gastro-Intestinal Diseases, Department of Physiology, Michael Reese Hospital.

1. Hunt, R., and Taveau, R. de M.: *Brit. M. J.* 2:1788, 1906.

siderable attention, notably from Hunt and his collaborators in this country and in the laboratory of Dale and his co-workers in England. These studies have tended to show that acetylcholine or its precursor is normally present in the body, that it is liberated whenever parasympathetic nerves are stimulated and that when injected, even in infinitesimal doses, it elicits parasympathetic effects. Dale and his group<sup>2</sup> (1914-1915) studied the stimulating effect of acetylcholine and of other choline esters on the motility of the gastro-intestinal tract. Guggenheim and Loeffler<sup>3</sup> (1916) were able to find choline in the blood of normal persons. Feldberg and Rosenfeld<sup>4</sup> (1933) found acetylcholine in the blood of the mesenteric veins, and Dale and Feldberg<sup>5</sup> (1934) found it in the perfusion fluid of the stomach. Magnus and Le Heux<sup>6</sup> (1918 to 1921) considered choline to be the hormone inducing intestinal motility, and Abderhalden and Pfaffrath<sup>7</sup> (1926) found that the intestine contains an esterase which is able to acetylyze choline, thus producing a compound which is many times more potent than choline itself.

Attempts have been made to use choline and acetylcholine in the treatment of experimental paralytic ileus. Kühlewein,<sup>8</sup> in Magnus' laboratory (1921), reported that she paralyzed gastro-intestinal motility in cats by prolonged chloroform anesthesia and that she was able to reestablish peristaltic activity by the intravenous injection of from 5 to 15 mg. of choline per kilogram of body weight. Arai<sup>9</sup> (1922) produced peritonitis in anesthetized cats in several ways, including the injection of tincture of iodine and of bacterial emulsions into the peritoneal cavity. He observed that fluoroscopically, after a barium sulfate meal, increased peristalsis could be demonstrated after the injection of 10 mg. of choline hydrochloride per kilogram of body weight.

Carlson<sup>10</sup> (1927) injected choline into normal dogs and found increased tonus and peristalsis in only a few of his experiments. Kahlson<sup>11</sup> (1933) found that the intestinal wall produces choline and that choline is necessary for the occurrence of peristalsis, although it does not produce it directly.

Choline and its compounds have been used therapeutically in clinical cases of ileus. Klee and Grossman<sup>12</sup> (1923) injected intravenously 600

2. Dale, H. H.: *J. Pharmacol. & Exper. Therap.* **6**:147, 1914-1915.

3. Guggenheim, M., and Loeffler, W.: *Biochem. Ztschr.* **74**:208, 1916.

4. Feldberg, W., and Rosenfeld, P.: *Arch. f. d. ges. Physiol.* **232**:212, 1933.

5. Dale, H. H., and Feldberg, W.: *J. Physiol.* **81**:320 (June 9) 1934.

6. Le Heux, J. W.: *Arch. f. d. ges. Physiol.* **173**:8, 1918; **179**:177, 1920; **190**:301, 1921.

7. Abderhalden, E., and Pfaffrath, H.: *Fermentforsch.* **8**:284 and 294, 1925.

8. Kühlewein, M.: *Arch. f. d. ges. Physiol.* **191**:99, 1921.

9. Arai, K.: *Arch. f. exper. Path. u. Pharmakol.* **94**:149, 1922.

10. Carlson, A. J.; Smith, E., and Sibbins, I.: *Am. J. Physiol.* **81**:435, 1927.

11. Kahlson, G.: *Klin. Wehnschr.* **12**:1015, 1933.

12. Klee and Grossman: *München. med. Wehnschr.* **18**:581, 1923.

mg. of choline prepared in Magnus' laboratory and reported favorable results. Spatz and Wichmann<sup>13</sup> (1924) used choline in twenty-one patients. They found that it stimulated motility in a few cases, frequently inhibited motility and had a toxic effect even in small doses. Wolff and Canney<sup>14</sup> (1926) reported good therapeutic results in three cases in which they slowly injected 600 mg. of choline intravenously. Abel<sup>15</sup> (1933) utilized acetylcholine as a prophylactic measure to prevent the development of postoperative ileus after abdominal operations. He injected 100 mg. of acetylcholine intravenously thirty-six hours after operation and repeated the dose every two or three hours. Usually two or three injections were sufficient to produce a bowel movement, and in none of a series of fifty abdominal operations did ileus develop. He considered acetylcholine a specific in postoperative ileus and recommended its use as a routine procedure.

Physostigmine salicylate has long been used in the treatment of postoperative ileus. Fröhner<sup>16</sup> stated in his textbook (1900) that physostigmine had been in common use in the treatment of ileus and of gastrointestinal atonia in animals. Cushny<sup>17</sup> reported good results from its use in the treatment of intestinal atony in man. Cannon and Murphy<sup>18</sup> (1907) stated that they produced ileus in anesthetized dogs by crushing the testes and were able to relieve it with physostigmine. Ochsner, Gage and Cutting<sup>19</sup> reported similar results, but their control experiments on normal dogs showed no increased motility after the administration of physostigmine.

Fuehner<sup>20</sup> (1918) found that the effects of acetylcholine in causing contractions of the back muscle of the leech were tremendously increased by the addition of physostigmine. Reid Hunt<sup>21</sup> (1917) described a similar fortification of the various effects of acetylcholine by physostigmine. He postulated the theory that this potentiation was due to the inhibition of an esterase which under normal conditions rapidly destroys acetylcholine. Matthes<sup>22</sup> (1930) and Loewi and Engelhart<sup>23</sup> (1930) sub-

13. Spatz, H., and Wichmann, E.: München. med. Wchnschr. **41**:1425, 1924.

14. Wolff, C. G. H., and Canney, J. R.: Lancet **1**:707, 1926.

15. Abel, A. L.: Lancet **2**:1247, 1933.

16. Fröhner, E.: Toxicologie für Tierärzte, Stuttgart, Ferdinand Enke, 1900.

17. Cushny, A. R.: A Text-Book of Pharmacology and Therapeutics or the Action of Drugs in Health and Disease, ed. 10, Philadelphia, Lea & Febiger, 1934.

18. Cannon, W. B., and Murphy, F. T.: Physiologic Observations on Experimentally Produced Ileus, J. A. M. A. **49**:840 (Sept. 7) 1907.

19. Ochsner, A.; Gage, I. M., and Cutting, R. A.: Value of Drugs in Relief of Ileus, Arch. Surg. **21**:924 (Dec., pt. 1) 1930.

20. Fuehner, H.: Arch. f. exper. Path. u. Pharmakol. **82**:51 and 205, 1918.

21. Hunt, R.: Am. J. Physiol. **45**:231, 1918.

22. Matthes, K.: J. Physiol. **70**:338, 1930.

23. Loewi, O., and Engelhart, E.: Arch. f. exper. Path. u. Pharmakol. **150**: 1, 1930.



sequently proved the correctness of this hypothesis and showed that this inhibition of the specific esterase was effective in dilutions of physostigmine as high as 1:40,000,000. With a small amount of physostigmine, acetylcholine can be demonstrated in the circulating blood. This inhibitory action is specific for eserine and is not possessed in comparable strength by any of the related alkaloids. The effect of physostigmine can be reversed by dialysis; so it may be assumed that the combination of physostigmine and esterase is a loose one. To our knowledge, the only clinical use of a combination of acetylcholine and physostigmine has been the work of Carmichael and Fraser<sup>24</sup> (1933), who administered both drugs intravenously to patients with diseases of the circulatory system but were not satisfied with the results.

There are several other choline esters which exhibit a similar pharmacologic effect but which are not hydrolyzed by the esterase. They are therefore more stable and apparently are preferable to the acetylcholine-physostigmine mixture for stimulating peristaltic activity. One such ester, acetyl-beta-methylcholine, was studied by Reid Hunt as early as 1911. This preparation has recently received considerable attention from Starr and his associates<sup>25</sup> (1933) and from Simonart<sup>26</sup> (1933) and is now available commercially. These investigators found acetyl-beta-methylcholine decidedly more effective than acetylcholine because of its greater stability. In experiments on dogs and cats, Comroe and Starr found that acetyl-beta-methylcholine increased peristalsis and tonus of the intestine. Starr and his co-workers injected from 5 to 15 mg. of acetyl-beta-methylcholine subcutaneously in normal human subjects and reported increased peristaltic activity of the entire gastrointestinal tract. This action was accompanied, however, by disagreeable side-effects, including salivation, flushing and abdominal pain. The oral administration of from 200 to 600 mg. yielded marked peristaltic effect without associated symptoms. Abbott<sup>27</sup> (1933) used acetyl-beta-methylcholine for patients with surgical ileus. Control tests on normal persons, with subcutaneous injection of from 5 to 20 mg. of acetyl-beta-methylcholine, produced increased tonus and peristalsis of the stomach, duodenum and colon.

From this review of the literature, it is seen that acetylcholine is the physiologic stimulant of peristaltic activity, that it is quickly destroyed by the blood and tissues and that its destruction is prevented

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24. Carmichael, E. A., and Fraser, A. R.: *Heart* **16**:263, 1933.

25. Comroe, J. H., and Starr, I.: *J. Pharmacol. & Exper. Therap.* **49**:283, 1933.

26. Simonart, A.: *J. Pharmacol. & Exper. Therap.* **46**:157, 1932.

27. Abbott, W. O.: *Am. J. M. Sc.* **186**:323, 1933.

for a relatively long period by minute concentrations of physostigmine. Physostigmine furthermore intensifies the action of acetylcholine, permitting a striking reduction in the effective dosage of the latter drug. Other choline esters, notably the acetyl-beta-methylcholine, possess a similar action but are much more stable, and hence more effective, than acetylcholine. For these reasons it seemed reasonable to study the effect of acetylcholine in combination with physostigmine in combating intestinal atonia and to compare its action with that of acetyl-beta-methylcholine.

#### EXPERIMENTAL METHODS

The experiments were conducted on dogs under light ether anesthesia. Blood pressure was registered by means of a cannula in the carotid artery, in the usual way. Rubber balloons were introduced into the stomach, small intestine and colon and connected with water manometers, and the abdominal wound was closed. The body temperature was maintained by a heated operating table. Slow, constant intravenous infusions of 1 per cent of dextrose in a physiologic solution of sodium chloride were given throughout the course of the experiments, at the rate of about 35 cc. per hour, by means of a constant injection pump. Studies of gastro-intes-

TABLE 1.—*Types of Motility*

Excursion of Manometer, Cm.	Type of Motility
0.....	0
0 to 1.....	1
1 to 5.....	2
5 to 10.....	3
Above 10.....	4

tinal motility were made in normal animals and in dogs in which the development of paralytic ileus was attempted by the production of peritonitis and by other measures which are supposed to result in intestinal paralysis. The results of these efforts will be described below.

The drugs used were acetylcholine, physostigmine salicylate and acetyl-beta-methylcholine.<sup>27a</sup> The injections were given intramuscularly or intravenously. Before each injection, the motility of the intestine was recorded for from one half to one hour as a control period. Injections were given when tonus and peristalsis were regular and minimal. The motility in these experiments is expressed in four grades, according to the height of excursion of the water manometer (table 1).

*Experiments in Normal Animals.*—A. Physostigmine, Acetylcholine and Physostigmine and Acetylcholine: A preliminary report of these experiments has been made.<sup>28</sup> Physostigmine salicylate was used alone, by intramuscular injection, in doses of from 0.5 to 3 mg. It was found that quantities less than 1 mg. usually produced no recognizable effect on gastro-intestinal motility. Doses above 1.5 mg.

27a. Hoffmann-La Roche supplied the acetylcholine and Merck & Co. supplied the acetyl-beta-methylcholine used in this work.

28. Frank, R.; Zimmerman, L. M., and Necheles, H.: *Proc. Soc. Exper. Biol. & Med.* **32**:686, 1935.

often caused undesirable concomitant effects, such as excessive salivation, increased respiration and a tetanic contraction of the intestine. One milligram of physostigmine salicylate did not cause these undesirable effects, but a demonstrable increase in gastro-intestinal peristalsis was seen in only 50 per cent of the experiments.

The intramuscular injection of 0.025 mg. of acetylcholine alone had no demonstrable effect on blood pressure or on intestinal motility. When this quantity of acetylcholine was combined with 1 mg. of physostigmine salicylate, a slight drop in blood pressure, of from 10 to 15 mm. of mercury, occurred, which disappeared after from 2 to 3 minutes. As will be seen in table 2, this combination produced peristalsis in the stomach, small intestine and colon in almost all the animals.

TABLE 2.—*Effect of Intramuscular Injection of Physostigmine (1 mg.) and of Physostigmine (1 mg.) Plus Acetylcholine (0.025 mg.) on Gastro-Intestinal Motility*

	Stomach		Ileum		Colon	
	Physo- stigmine	Physo- stigmine plus Acetyl- choline	Physo- stigmine	Physo- stigmine plus Acetyl- choline	Physo- stigmine	Physo- stigmine plus Acetyl- choline
Increased peristalsis.....	8	12	6	11	10	13
No effect.....	8	2	10	3	6	1

B. Acetyl-Beta-Methylcholine: A dose of 0.1 mg. of acetyl-beta-methylcholine given intramuscularly caused a drop of blood pressure of from 20 to 60 mm. Most of the dogs did not recover from this injection and died of circulatory failure, but there was no effect on gastro-intestinal motility. Rectal injection of 600 mg. of acetyl-beta-methylcholine was ineffective. Oral administration was not tried because this route would probably not be available in cases of paralytic ileus.

*Experiments in Animals with Paralytic Ileus.*—Attempts were made to produce a state of paralytic ileus in dogs comparable to that which occurs in man and to determine the effect of the acetylcholine-physostigmine mixture on gastro-intestinal motility under those conditions. The following measures were tried:

A. Induction of peritonitis with croton oil. A mixture of croton oil in olive oil was injected into the peritoneal cavity. Ten cubic centimeters of the mixture contained 1 drop of croton oil, and, according to the size of the animal, from 10 to 15 cc. of this mixture was injected. Peritonitis developed rapidly. In from one to three hours the abdominal cavity contained from 100 to 200 cc. of hemorrhagic fluid, and the serous surfaces of the gastro-intestinal tract were markedly injected and covered with a fibrinous exudate. The peritonitis was so severe that if the croton oil mixture was injected the night before the experiment the animal often died before morning or was so sick that it did not survive the anesthesia and the preliminary steps of the experiments.

B. Induction of peritonitis with aqueous solution of iodine U. S. P. Twenty-four hours before the experiment, from 7 to 25 cc. of compound solution of iodine U. S. P. (Lugol's solution) was injected intraperitoneally, and immediately before

the experiment from 10 to 30 cc. was given, depending on the intensity of the peritonitis present and the degree of intestinal atonia.

C. Induction of peritonitis with iodine. From 10 to 50 cc. of 5 per cent tincture of iodine was injected intraperitoneally before the experiment.

D. Induction of peritonitis with bile. From 10 to 30 cc. of dog's bile was injected intraperitoneally before the experiment.

E. Induction of peritonitis with the colon bacillus. Injection of washings of cultures of *Bacillus coli* was made intraperitoneally before the experiment.

F. Induction of peritonitis with feces. Injection of an emulsion of dog's feces was made intraperitoneally, twenty-four hours before the experiment.

G. Trauma to the gastro-intestinal tract, crushing of the testes, high aseptic ligation of the jejunum twenty-four hours before the experiment and prolonged chloroform anesthesia.

We were unable to produce a complete and generalized paralytic ileus comparable to that which is seen in human beings. In spite of the long list of methods enumerated, all of which have been reported by others to result in intestinal paralysis, we succeeded in causing at best only a relative paresis. This relative ileus consisted of prolonged periods of quiescence and atony of the gastro-intestinal tract, which were followed by phases of more or less vigorous contraction. These extended intervals of quiescence and atony were used in our experimental efforts to stimulate motility and tonus. Complete atony of the gastro-intestinal tract was often observed in the terminal stages of peritonitis, when the blood pressure had fallen and the dog was moribund. Animals in this condition could not be used for testing effects of the drugs.

Since we found croton oil to be the most uniformly effective and reliable agent in producing peritonitis and with it a relative paralytic ileus, we are presenting only those experiments in which this substance was used. Ten experiments were done on nine dogs. All injections were given intramuscularly. As in the previous series, physostigmine and acetylcholine were first tried alone and then the two drugs in combination. No gastro-intestinal motility could be induced by small doses of acetylcholine alone (from 0.01 to 0.02 mg.), and only inconstant effects were produced by small doses of physostigmine (up to 1 mg.). These results are similar to those found by us<sup>28</sup> in normal animals.<sup>29</sup> The response to 0.02 mg. of acetylcholine and 1 mg. of physostigmine injected together in the dogs with peritonitis was greater than that to 0.025 mg. of acetylcholine and 1 mg. of physostigmine in the normal animals. The latent period was somewhat shorter than that in normal animals. There was no significant drop in blood pressure or change

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29. Ellis and Weiss reported that man is more resistant to acetylcholine than are animals (*J. Pharmacol. & Exper. Therap.* **44**:235, 1932).

TABLE 3.—*Effect of Acetylcholine and Physostigmine on Gastro-Intestinal Motility in Peritonitis*

Ex- peri- ment	Dose, Mg.		Latent Period in Minutes		Increased Motility				Blood Pressure After Injection	Comment					
	Acetyl- choline	Physo- stig- mine	Stom- ach	Small Intestine	Stomach		Small Intestine								
					Minutes	Type	Minutes	Type							
1	0.02	1	20	15	8	Increased tone	30	Increased tone	20	1	60	2 to 3	No change		
						0							2-		
						Increased tone							4 to 3	No change	
2	0.01	1	15	10	5	4	2	4	40	4 to 3	110	4 to 3	No change		
3	0.02	1	5	10	1	Increased tone	60	Increased tone	50	2 to 4	60	2 to 3	No change		
4	0.01	2	5	5	5	2 to 4 and Increased tone	75	2 to 4 and Increased tone	75	2 to 3 and Increased tone	75	2 to 3 and Increased tone	No change		
{ <sup>a</sup> 5 { <sup>b</sup>	0.01	2	5	5	..	2 to 3 and Increased tone	35	2 to 3 and Increased tone	80	2 to 3 and Increased tone	..	..	No change	Panting after injection	
	0.01	3	10	3	..	3 to 4	30	3 to 4	25	2 to 3	..	..	No change		
6	0.01	3	2	2	2	2 to 3 and Increased tone	60	2 to 3 and Increased tone	60	1 to 2	60	2 and Increased tone	Drop; death after 60 minutes		
7	0.01	3	5	3	4	Increased tone	55	Increased tone	50	Increased tone	50	3 to 4 and Increased tone	No change		
8	0.01	3	5	5	5	Increased tone	25	Increased tone	30	3 and Increased tone	15	1 to 2	No change	Panting after injection	
9	0.01	3	12	5	5	1 to 2 and Increased tone	15	1 to 2 and Increased tone	40	4	30	3 to 4	No change		

in respiration following the injection of the combination of drugs with doses of physostigmine of from 1 to 2 mg. Owing to the severity of the peritonitis and the prolonged duration of the experiments, there was, however, a slow and gradual decline in blood pressure.

#### COMMENT

In these experiments we attempted to stimulate gastro-intestinal motility by means of acetylcholine, which is apparently the physiologic agent of peristaltic activity of the digestive tract. In order to obtain the full effect of this mechanism it was necessary to give it in combination with physostigmine, which inhibits the rapid destruction of acetylcholine in the fluids and tissues of the body. In normal animals, we found that small doses of physostigmine alone, in quantities up to 1 mg., had no effect on blood pressure or other bodily functions, as far as we were able to ascertain, and only inconstant effect on gastro-intestinal motility. Small doses of acetylcholine, which alone were incapable of stimulating gastro-intestinal motility did produce peristaltic activity when combined with physostigmine, and caused little or no change in blood pressure. In dogs with peritonitis, physostigmine in doses of 1 mg. combined with from 0.01 to 0.02 mg. of acetylcholine produced a greater degree of gastro-intestinal motility than they did in the normal animals. Increasing the quantity of physostigmine, with the smaller doses of acetylcholine, did not appreciably increase the peristaltic effect (table 2, experiments 1 to 3 and 4 to 9).

The effectiveness of the acetylcholine-physostigmine mixture in the animals with peritonitis suggests its clinical use in cases of paralytic ileus. Acetyl-beta-methylcholine was discontinued in our studies because when injected it apparently had more pronounced effects on the cardiovascular system than on the gastro-intestinal tract. Starr and Comroe stated that the cardiovascular effects of acetyl-beta-methylcholine are mild or absent after oral administration, but as we were seeking an agent to use in conditions with paralytic ileus which might preclude the oral route, a substance which could be injected was necessary. In one experiment, relatively large doses of acetyl-beta-methylcholine were not effective when given by rectum.

#### SUMMARY

Acetylcholine, physostigmine and a combination of acetylcholine and physostigmine were tested as to their effect on the production of gastro-intestinal motility in normal dogs and in animals with experimental peritonitis.

Small doses of acetylcholine alone had very little or no effect on peristaltic activity in either group.

Small doses of physostigmine alone had inconstant effects on gastro-intestinal motility.

Intramuscular injection of small doses of physostigmine in combination with acetylcholine always produced increased gastro-intestinal motility, without significant cardiovascular disturbances or other undesirable manifestations.

Animals with peritonitis responded somewhat more to the acetylcholine-physostigmine mixture than did the normal ones.

Attempts were made to produce complete paralytic ileus by a number of different procedures. None were successful, except in the terminal stages, when the dogs were no longer in condition for experimentation. A relative ileus resulted from chemical peritonitis, which was characterized by prolonged periods of atony and quiescence. These atonic intervals were used in studying the effects of physostigmine and acetylcholine on gastro-intestinal motility in the presence of peritonitis.

# ALLERGY AS AN EXPLANATION OF DEHISCENCE OF A WOUND AND INCISIONAL HERNIA

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Dehiscence or disruption of a wound occurs with sufficient frequency to warrant the presentation of a symposium on this subject before the New York Surgical Society in 1933. Papers were read by members of the staffs of five hospitals in New York, and Meleney and Howes<sup>1</sup> reported 55 cases from the Presbyterian Hospital in an eight year period, or an incidence of 1 per cent. They thought that the diagnosis had been frequently omitted from the records if there had not been a secondary closure and that 2 per cent would more nearly represent the incidence of this catastrophe. Colp<sup>2</sup> reported 29 cases in 2,750 laparotomies, or an incidence of 0.9 per cent, from the Mount Sinai Hospital. Grace<sup>3</sup> reported 44 cases in a fifteen year period from the first surgical division of the Bellevue Hospital. White<sup>4</sup> reported 30 cases from the Roosevelt Hospital. Heyd<sup>5</sup> reported 4 cases in 1,000 laparotomies performed at the New York Post-Graduate Hospital in 1932 and 4 personal cases. There was a total of 166 cases reported at the meeting of the New York Surgical Society. Sokoloff<sup>6</sup> in 1931 reported the largest group of cases on record, numbering 725, based on the experience of 187 surgeons. He sent questionnaires to 1,140 European surgeons. Eliason and McLaughlin<sup>7</sup> reviewed 9,155 operations at the University of Pennsylvania Hospital and found 25 instances of dehiscence. Maes,

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1. Meleney, Frank L., and Howes, Edward L.: The Disruption of Abdominal Wounds with the Protrusion of the Viscera, *Ann. Surg.* **99**:5 (Jan.) 1934.

2. Colp, Ralph: Disruption of Abdominal Wounds, *Ann. Surg.* **99**:14 (Jan.) 1934.

3. Grace, Roderick V.: Disruption of Abdominal Wounds, *Ann. Surg.* **99**: 28 (Jan.) 1934.

4. White, William C.: Disruption of Abdominal Wounds, *Ann. Surg.* **99**: 34 (Jan.) 1934.

5. Heyd, Charles G.: Disruption of Abdominal Wounds, *Ann. Surg.* **99**:39 (Jan.) 1934.

6. Sokoloff, S.: Die postoperative Ruptur der Bauchwunde mit Hervortreten oder Vorfall der Eingeweide, *Vestnik khir.* (nos. 65-66) **22**:219, 1931.

7. Eliason, E. L., and McLaughlin, Charles: Post-Operative Wound Complications, *Ann. Surg.* **100**:1159 (Dec.) 1934.



Boyce and McFetridge<sup>8</sup> reported 44 cases in a ten year period at the Charity Hospital in New Orleans. Baldwin<sup>9</sup> reviewed his individual series and found that in the past thirty-five years he has not had a single instance of dehiscence in 16,465 operations. After one studies these reports as to the cause, prevention and treatment of this serious sequela of celiotomy, it is difficult to evaluate the opinions expressed by the different authors.

The foregoing reports convince one that the type of incision, the magnitude of the operation, the choice of the anesthetic or the type of closure plays only an insignificant part in dehiscence of the wound. Colp<sup>2</sup> summarized the subject by stating that the anesthetic, the type of wound closure and infection or drainage of the wound have little or no relation to the frequency of dehiscence. Meleney and Howes<sup>1</sup> stressed the importance of infection of the wound in cases of dehiscence but said that chronic catgut is completely absorbed in "clean cases" in which bacterial cultures are negative and whether the wound disrupts on the third or on the thirteenth postoperative day. There is a warning note by all authors as to the peculiar capacity of the tissues of some persons to digest catgut completely. Erdmann<sup>10</sup> referred to tissue hunger, which digests the gut too early. Colp<sup>2</sup> spoke of idiosyncrasy of the patient as a possible factor. White<sup>4</sup> referred to a predisposing factor for which a name cannot be given, and stated that the body tissue causes an early dissolution of the catgut in the absence of infection of the wound. Sokoloff<sup>6</sup> stressed the fact that in only 15.7 per cent of 725 cases was the wound infected. He was so amazed at the low incidence of infection that these cases were carefully rechecked to verify this point. Maes, Boyce and McFetridge<sup>8</sup> stressed infections of the respiratory tract as a cause, but this is not borne out in other reports. Other factors that have been stressed by different authors, such as distention, vomiting and chronic debilitating diseases with secondary anemia, are not borne out as real factors when one carefully analyzes a large series of cases.

A review of the reports of the different authors reveals that they have not stressed the fact that dehiscence of the wound in all probability is a more advanced stage of the same process that produces incisional hernia and causes inguinal hernia to recur after the many different methods of repair that have been advocated.

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8. Maes, Urban; Boyce, Frederick, and McFetridge, Elizabeth: Post-Operative Evisceration, *Ann. Surg.* **100**:968 (Nov.) 1934.

9. Baldwin, J. F.: Disruption of Abdominal Wounds, *Am. J. Surg.* **25**:7 (July) 1934.

10. Erdmann, John F.: The Recognition and Treatment of Post-Operative Complications, *South. Surgeon* **11**:193 (Sept.) 1933.

To have a clear conception of the complete picture of dehiscence of the wound it would seem justifiable to divide it into three stages. Stage 1 consists of complete separation of the peritoneum and the posterior sheath of the rectus abdominis muscle with incomplete separation of the anterior sheath of the rectus abdominis muscle. In such cases the wound heals by primary union, with the exception of a slight serosanguineous discharge on from the fifth to the eighth day. The discharge is usually attributed to a hematoma, but if the wound is not tightly strapped to reenforce the entire abdominal layers, an incisional hernia is most likely to occur. A follow-up study of cases of this type reveals a high incidence of incisional hernia after from six to twelve months. Stage 2 consists of complete separation of the entire abdominal layers without protrusion of an abdominal viscus. Stage 3 consists of complete separation of the abdominal layers with protrusion of an abdominal viscus.

It would seem that an analysis of 19 cases occurring in the experience of one person might help to throw some light on many of the points under discussion in regard to dehiscence of a wound. For that reason a résumé of 19 instances of dehiscence occurring in 621 laparotomies in the past thirteen years, or an incidence of 3.05 per cent, will be presented.

#### REPORT OF CASES

CASE 1.—A man aged 40 was admitted to the New York Post-Graduate Medical School and Hospital in November 1923, for cholecystitis and cholelithiasis. A cholecystectomy and appendectomy were performed with the patient under ether anesthesia. A cigaret drain was inserted to the gallbladder fossa. The peritoneum was closed with a continuous suture of no. 2 plain catgut, and the fascia, with a continuous suture of no. 2 chromic catgut. Four retention sutures of silkworm gut were used beneath the fascia, and the skin was closed with a silk suture.

On the fifth postoperative day there was a moderate amount of serosanguineous discharge, which completely saturated the dressing and necessitated the dressing of the wound twice daily for the next three days, after which there was a moderate amount of discharge for three more days. The patient left the hospital on the twentieth day. The dehiscence was of the stage 1 type.

Bronchitis of moderate severity developed, with only a slight cough. With the exception of the serosanguineous discharge and cough, the patient's convalescence was uninterrupted. A small incisional hernia was noticed six months after he left the hospital, and it gradually enlarged in spite of the fact that he wore an abdominal belt. In February 1930 he was readmitted to the hospital and operated on for the hernia, a Gallie fascial repair being done. He has been cured since this operation.

CASE 2.—A man aged 43 was admitted to the Bellevue Hospital in October 1924, with a perforated duodenal ulcer. A Horsley pyloroplasty was performed

with the patient under ether anesthesia. The peritoneum was closed without drainage with a continuous suture of no. 2 plain catgut, and the fascia was closed with a continuous suture of no. 2 chromic catgut. Three retention sutures of silkworm gut were used beneath the fascia, and the skin was closed with a silk suture.

On the sixth postoperative day there was a serosanguineous discharge on the dressing, and on the seventh day the wound had partly separated, with the small intestine protruding. The patient was taken to the operating room, and the wound was closed as before. Firm union resulted in fourteen days. The dehiscence was of the stage 3 type.

The postoperative course in this case was uneventful. The patient did not suffer from distention and did not vomit, and there were no pulmonary complications. The wound was not infected, and primary union resulted after the second closure. The patient was readmitted to the hospital in 1927 with acute appendicitis. He was operated on by me, and the original scar was firm at that time.

CASE 3.—A man aged 48 was admitted to the Bellevue Hospital in June 1925 with a perforated duodenal ulcer. A Horsley pyloroplasty was performed with the patient under ether anesthesia. The peritoneum was closed without drainage with a continuous suture of no. 2 plain catgut, and the fascia was closed with a continuous suture of no. 2 chromic catgut. Three retention sutures of silkworm gut were used beneath the fascia, and the skin was closed with a silk suture.

On the seventh postoperative day the dressing was saturated with a serous discharge, and when the wound was inspected and the silk sutures removed, the small intestine was found lying beneath the skin. The patient was immediately reoperated on, and the wound was closed as formerly. The wound became infected but healed in thirty days after the second closure. The dehiscence was of the stage 2 type.

The patient's convalescence was uninterrupted up to the time of dehiscence of the wound. There was no evidence of infection at the time of the second closure, but in spite of a severe infection an incisional hernia did not occur. Pyloric stenosis developed, and gastro-enterostomy was performed in September 1927. The patient has been followed in the "stomach clinic" of the fourth surgical division since, and the wounds are firm at the time of writing.

CASE 4.—A woman aged 45 was admitted to the Bellevue Hospital in October 1927, with acute cholecystitis and cholelithiasis. A cholecystectomy was done with the patient under ether anesthesia. A cigaret drain was inserted to the gallbladder fossa. The peritoneum was closed with a continuous suture of no. 2 plain catgut, and the fascia with a continuous suture of no. 2 chromic catgut. Three retention sutures of silkworm gut were used beneath the fascia, and the skin was closed with a silk suture.

On the fifth postoperative day there was a serosanguineous discharge, which persisted until the seventh day, and then the edges of the skin were partly separated. On removing the silk suture, the wound was found to be completely separated, but no viscus was protruding. The wound was closed as originally. A slight infection resulted, but the wound was healed in twenty days following the second operation. The dehiscence was of the stage 2 type.

There was a slight cough for four days, but the convalescence was otherwise uninterrupted. The wound was clean at the time of dehiscence. The patient left the hospital twenty days after the second closure, and the wound was firm. She has not been followed.

CASE 5.—A man aged 35 was admitted to the New York Post-Graduate Medical School and Hospital in January 1928, with acute cholecystitis, cholelithiasis and acute appendicitis. A cholecystectomy and an appendectomy were done with the patient under ether anesthesia. A cigaret drain was inserted to the gallbladder fossa. The peritoneum was closed with a continuous suture of no. 2 plain catgut, and the fascia with a continuous suture of no. 2 chromic catgut. Four retention sutures of silkworm gut were used beneath the fascia, and the skin was closed with a silk suture.

On the sixth postoperative day there was a moderate serosanguineous discharge. The wound was strapped with adhesive tape, and the sutures were not removed from the skin as the patient was an apprehensive lawyer. The wound apparently healed by primary union, and the patient left the hospital on the twentieth postoperative day. A small incisional hernia soon developed. At the time this paper is written the patient has a large hernia which needs to be repaired. The dehiscence was of the stage 1 type.

I feel that if the sutures had been removed at the time the discharge was noted the wound would have separated. If an immediate repair had been done a hernia might possibly have been prevented.

CASE 6.—A woman aged 33 was admitted to the Bellevue Hospital in April 1928, for cholecystitis and cholelithiasis. She was operated on under spinal anesthesia and found to have a large echinococcus cyst of the liver, located between the gallbladder and the surface of the liver and partly embedded in the substance of the liver. The cyst was completely enucleated, and a cholecystectomy was done. The abdomen was drained with iodoform gauze. The peritoneum was closed with a continuous suture of no. 2 plain catgut, and the fascia, with a continuous suture of no. 2 chromic catgut and five interrupted sutures of chromic catgut. Five retention sutures of silkworm gut were used beneath the fascia, and the skin was closed with a silk suture.

The postoperative course was marked by pleurisy on the right side with effusion, which necessitated two aspirations. The patient was critically ill for several days. There was complete dehiscence of the wound on the eighth day. The patient was very ill, so the wound was merely strapped and was dressed several times a day. It healed on the forty-fifth day, and the patient was discharged without a hernia. There was a moderate infection of the wound. The dehiscence was of the stage 2 type.

The patient has been seen on numerous occasions since leaving the hospital, and there is no evidence of a hernia.

CASE 7.—A man aged 39 was admitted to the Bellevue Hospital in August 1929. He was referred from the "stomach clinic" with a chronic duodenal ulcer. The ulcer was excised and a gastro-enterostomy was performed, spinal anesthesia being used. The peritoneum was closed with a continuous suture of no. 2 plain catgut, and the fascia, with a continuous suture of no. 2 chromic catgut. Three retention

sutures of silkworm gut were used beneath the fascia, and the skin was closed with a silk suture.

On the sixth postoperative day the wound was saturated with a serosanguineous discharge, and on removing the sutures from the skin the wound was found to be completely separated, but no viscus protruded on the abdomen. The wound was closed as originally. A moderate degree of infection developed after the second closure, but the wound completely healed in twenty-four days. The dehiscence was of the stage 2 type.

There were no complications in this case during convalescence to account for the dehiscence of the wound. The patient has been followed in the "stomach clinic," and the wound is firm at the time of writing.

CASE 8.—A man aged 42 was admitted to the Bellevue Hospital in August 1929. He was referred from the "stomach clinic" with a chronic duodenal ulcer with recurring hemorrhages. The ulcer was excised, and a gastro-enterostomy was performed with the patient under spinal anesthesia. As the patient in case 7 had been operated on one week before, it was decided to use a different make of catgut. The peritoneum was closed with a continuous suture of no. 2 plain catgut to which were added five interrupted sutures of plain catgut. The fascia was closed with a suture of continuous no. 2 chromic catgut and also reenforced with interrupted sutures of chromic catgut. Three retention sutures of silkworm gut were used beneath the fascia, and the skin was closed with a silk suture.

On the seventh postoperative day the dressing was saturated with a serous discharge. When the silk sutures were removed, the omentum protruded on the abdomen. The patient was operated on under spinal anesthesia, and the wound was closed with through-and-through sutures of silkworm gut. The wound healed on the fourteenth day without infection. The dehiscence was of the stage 3 type.

The patient had a definite bronchitis but not true pneumonia. Since his discharge he has been followed in the clinic, and his wound has remained firm.

CASE 9.—A woman aged 53 was admitted to the Bellevue Hospital in August 1929, with cholecystitis and cholelithiasis. Cholecystectomy was performed with the patient under spinal anesthesia. A cigaret drain was inserted to the gall-bladder fossa. As the patient was operated on the same day that the wound of the patient in case 8 was resutured, I was more than concerned about the closure. Still a different make of catgut was used, and the peritoneum was closed with interrupted sutures of no. 2 plain catgut. The sutures were placed  $\frac{1}{4}$  inch (0.6 cm.) apart. The fascia was closed in a like manner with no. 2 chromic catgut. Four retention sutures of silkworm gut were used beneath the fascia, and the skin was closed with a silk suture.

On the eighth postoperative day there was a serosanguineous discharge, and when the sutures were removed from the skin the wound was found to be completely separated. The wound was resutured with through-and-through sutures, spinal anesthesia being used. Healing occurred in twenty days with a slight infection. The dehiscence was of the stage 3 type.

There were no postoperative complications in this case and no evidence of infection at the time of the dehiscence. The wound was firm on the day of discharge, twenty days after the second closure.

CASE 10.—A man aged 37 was admitted to the Bellevue Hospital in September 1930, with a chronic duodenal ulcer. A posterior gastro-enterostomy and an appendectomy were done with the patient under spinal anesthesia.

The convalescence was uninterrupted, and the patient was out of bed on the thirteenth postoperative day, with apparently primary union of the wound. That night he complained of a sensation of warmth and of something giving away. When the wound was dressed, complete separation was found, with the small intestine protruding on the abdomen. He was operated on under spinal anesthesia, and the intestine was replaced. The wound was closed with through-and-through sutures of silkworm gut. The wound healed without any evidence of infection, and the patient was discharged from the hospital eighteen days later. The dehiscence was of the stage 3 type.

The patient's convalescence both before and after the first and second operations was uninterrupted, and there was no evidence of infection of the wound.

CASE 11.—A man aged 34 was admitted to the New York Post-Graduate Medical School and Hospital in February 1931, because of a chronic duodenal ulcer. The ulcer was excised and a posterior gastro-enterostomy and appendectomy were done with the patient under ether anesthesia. The peritoneum was closed with a continuous suture of no. 2 plain catgut and reenforced with three interrupted sutures. The fascia was closed with a continuous suture of no. 2 chromic catgut and reenforced with interrupted sutures. Three retention sutures of silkworm gut were used for the fascia, and the skin was closed with a silk suture.

The patient had an uninterrupted convalescence until the seventh day, when the dressing was saturated with a serosanguineous discharge. This necessitated the dressing of the wound twice a day for the next three days and once daily for four more days. With the exception of the discharge, the wound apparently healed by primary union, and the patient left the hospital on the eighteenth day. When he was reexamined three months after leaving the hospital there was evidence of a small incisional hernia. He has worn an abdominal belt, and the hernia has gradually enlarged. At the time of writing he has a large incisional hernia which should be operated on. There was no infection of the wound in this case, and no complications to account for the dehiscence, which was one of the stage 1 type.

CASE 12.—A man aged 37 was admitted to the Park West Hospital in May 1932 for a carcinoma of the stomach. Resection of the stomach and an anticolonic Polya anastomosis was done with the patient under ether anesthesia. The peritoneum was closed with a continuous suture of no. 2 plain catgut and reenforced with interrupted sutures. The fascia was closed with a continuous suture of no. 2 chromic catgut and reenforced with interrupted sutures. Three retention sutures of silkworm gut were used, and the skin was closed with a silk suture.

The patient's convalescence was uninterrupted until there was a serosanguineous discharge on the eighth day with a complete separation of the wound. The wound was resutured with through-and-through sutures, ether anesthesia being used. The patient made an uninterrupted convalescence and was discharged from the hospital sixteen days later. The dehiscence was of the stage 2 type.

There was no evidence of pulmonary complications or of infection of the wound to account for the dehiscence. The patient has been followed since leaving the hospital, and he is well, without any evidence of incisional hernia.

CASE 13.—A man aged 38 was admitted to the Bellevue Hospital in January 1932, with a duodenal ulcer which had perforated into the liver and had necessitated an operation six months previously. Operation was performed with the patient under ether anesthesia, and he was found to have a large duodenal ulcer which had perforated into the liver and was difficult to free. Subtotal resection of the stomach and an anticolic Polya anastomosis were done. The peritoneum was closed with a continuous suture of no. 2 plain catgut and reenforced with four interrupted sutures of no. 2 plain catgut. The fascia was closed with a continuous suture of no. 2 chromic catgut and reenforced with four interrupted sutures of chromic catgut. Four retention sutures of silkworm gut were used beneath the fascia, and the skin was closed with a silk suture.

The patient was critically ill after the operation. He had definite evidence of peritonitis on the second postoperative day. On the fifth day the wound was infected and completely separated. The patient was acutely ill from extensive peritonitis at this time. The wound was strapped with adhesive tape, but the patient died on the seventh postoperative day as a result of generalized peritonitis. The dehiscence was one of the stage 2 type.

Death in this case was due to peritonitis, and the dehiscence of the wound did not cause the fatality.

CASE 14.—A woman aged 48 was admitted to the Bellevue Hospital in October 1933, with a chronic duodenal ulcer. Operation was performed with the patient under ether anesthesia and a chronic duodenal ulcer was found as well as a large mesenteric cyst near the ligament of Treitz, which was adherent to the transverse colon. The operation consisted in complete enucleation of the cyst, which was the size of a large grapefruit, but during the procedure the blood supply of the transverse colon was damaged, and it was necessary to make a lateral anastomosis between the ascending and the descending colon. The peritoneum was closed with a continuous suture of no. 2 plain catgut and reenforced with four interrupted sutures of plain catgut. The fascia was closed with a continuous suture of no. 2 chromic catgut and reenforced with four interrupted sutures. Three retention sutures of silkworm gut were used beneath the fascia, and the skin was closed with a silk suture.

The patient had a moderate amount of abdominal distention, but otherwise her convalescence was uninterrupted until the sixth postoperative day, when there was a serosanguineous discharge. The sutures were removed from the skin, and the wound beneath the skin was found to be completely separated. The wound was resutured with through-and-through sutures of silkworm gut, ether anesthesia being used. The patient's convalescence was uninterrupted, and she left the hospital on the eighteenth postoperative day. The dehiscence was of the stage 2 type.

The patient's wound was not infected at the time of the dehiscence, but a slight infection resulted after the second closure. She was followed in the "stomach clinic" of the Bellevue Hospital for a few months but failed to return. In March 1935 she was readmitted to the hospital with a tremendous incisional hernia.

CASE 15.—A woman aged 43 was admitted to the Murray Hill Sanatorium in February 1933, with a diagnosis of duodenal obstruction. Operation with the patient under ether anesthesia revealed the stomach to be markedly dilated from a chronic duodenal obstruction, and a gastro-enterostomy was performed. The

peritoneum was closed with a continuous suture of no. 2 plain catgut but was not reenforced with interrupted sutures. The fascia was closed with a continuous suture of no. 2 chromic catgut, but was not reenforced with sutures of chromic catgut. Retention sutures of silkworm gut were used beneath the fascia, and the skin was closed with a silk suture.

This patient's convalescence was uninterrupted until the sixth postoperative day, when there was profuse serosanguineous discharge. The sutures were not removed from the skin, but the wound was strapped. The wound healed by primary union, with the exception of the discharge. The patient left the hospital on the seventeenth postoperative day. The dehiscence was of the stage 1 type.

The patient has been followed by her attending physician, and an incisional hernia was noticed within three months of the time of her discharge from the hospital.

CASE 16.—A man aged 32 was admitted to the New York Post-Graduate Medical School and Hospital in July 1934, with a chronic duodenal ulcer. Sub-total resection of the stomach and an anticollic Polya anastomosis were done with the patient under ether anesthesia. The peritoneum was closed with a continuous suture of no. 2 plain catgut and reenforced with interrupted sutures of plain catgut. The fascia was closed with a continuous suture of no. 2 chromic catgut and reenforced with four interrupted sutures of chromic catgut. Four retention sutures of silkworm gut were used beneath the fascia, and the skin was closed with silk sutures.

The patient's convalescence was uninterrupted until the seventh postoperative day, when the wound was dressed and found to be clean. On the afternoon of the same day there was a profuse serosanguineous discharge, and when the sutures were removed from the skin the wound was found to be completely separated, and the intestine protruded on the abdomen. The patient was reoperated on under spinal anesthesia, and the abdomen was closed with through-and-through retention sutures of silkworm gut. A slight infection of the wound developed after the second closure, but the patient left the hospital sixteen days after the second operation. The dehiscence was of the stage 3 type.

The patient has been followed regularly since she left the hospital, and the wound is firm at the time this report is written.

CASE 17.—A woman aged 53 was admitted to the Bellevue Hospital in October 1934, with a diagnosis of cholecystitis and cholelithiasis. Cholecystectomy and choledochotomy was performed with the patient under ether anesthesia. The abdomen was closed with through-and-through retention sutures of silkworm gut.

The patient became critically ill after the operation. Generalized peritonitis developed, and on the fourth postoperative day there was a severe infection of the wound. The retention sutures of silkworm gut did not hold, and there was complete separation of the wound. The patient died on the sixth postoperative day. The dehiscence was of the stage 2 type.

The patient had diffuse peritonitis with a severe infection of the wound, and the peritonitis was the cause of the patient's death.

CASE 18.—A man aged 53 was admitted to the New York Post-Graduate Medical School and Hospital in February 1935, with carcinoma of the recto-



sigmoid. Operation with the patient under ether anesthesia revealed a large carcinoma, which was adherent to the base of the bladder. A one stage abdominoperineal resection was performed. The abdomen was closed with through-and-through retention sutures of silkworm gut.

Generalized peritonitis developed, and on the fourth postoperative day there was a severe infection of the wound. When some of the sutures were removed there was a protrusion of the small intestine. The patient died on the ninth postoperative day. The dehiscence was of the stage 3 type.

The patient's death was due to generalized peritonitis, and there was a marked infection of the wound which resulted in a dehiscence. Peritonitis was the cause of death.

CASE 19.—A man, aged 49 was admitted to the New York Post-Graduate Medical School and Hospital in March 1935, with a diagnosis of cholecystitis and cholelithiasis. Cholecystectomy was performed with the patient under ether anesthesia. The peritoneum was closed with a continuous suture of no. 2 plain catgut and reenforced with three interrupted sutures of plain catgut. The fascia was closed with a continuous suture of no. 2 chromic catgut and reenforced with two sutures of chromic catgut sutures. Four retention sutures of silkworm gut were used and the skin was closed with silk sutures.

The patient's convalescence was uninterrupted except for a moderate degree of distention, but on the sixth postoperative day there was a slight serosanguineous discharge. The wound was inspected and strapped, and I did not believe that there was complete dehiscence. On the eighth postoperative day there was still more discharge, and when the silk sutures were removed the upper third and the lower third of the wound had completely united, but there was a complete separation in the midthird and a portion of the omentum protruded on the abdomen. This was replaced in the abdomen, and the wound was tightly strapped with adhesive tape. The patient left the hospital twenty-one days after the operation. The dehiscence was of the stage 3 type.

The wound to date is firm, but it is impossible to state whether there will be an incisional hernia. There was no evidence of infection to account for the dehiscence.

#### COMMENT

An early diagnosis of this serious complication is most essential, and the one diagnostic feature is a serous or serosanguineous discharge. When this is profuse the patient may complain of feeling warm fluid on his abdomen or the bedding may be saturated from the discharge. When the discharge has been profuse, the condition is immediately detected, but in cases of only moderate serosanguineous discharge, unless the wound is carefully inspected daily, an early dehiscence might be easily overlooked. For that reason many wounds are considered to be healing by primary union when they have actually had a partial dehiscence. The condition is not detected by the house staff on dressing the wound, as they are not experienced in looking for such a condi-

tion and attribute the serosanguineous discharge to a hematoma, which is usually not true in a case of celiotomy.

Dehiscence of the wound carries a rather high mortality. Meleny and Howes found a mortality of 44 per cent, Colp of 28 per cent, Grace of 39 per cent, White of 55 per cent, Maes, Boyce and McFetridge of 26 per cent and Sokolov of 33 per cent. The mortality in the cases reported in this paper was 16.7 per cent. When the three fatalities are reviewed (cases 13, 17 and 18) it can be seen that the primary cause of death was diffuse peritonitis. The uncomplicated cases of dehiscence of the wound rarely cause death if one is constantly watching for the first signs of this tragedy.

Dehiscence of the wound has caused me more consternation than any other sequela of abdominal operation. Such a high percentage of dehiscence of the wound as compared to the reports from other clinics has caused me to adopt numerous methods of wound closure, as attested by the case reports. In view of this appalling number of cases I have used both continuous and interrupted sutures of catgut of different makes and have relied on both plain and chromic catgut with additional reinforcement from sutures of silkworm gut. The length of time the retention sutures are left in seems to have little effect, as in most cases dehiscence occurs about the seventh day, and this is before retention sutures are removed. Baldwin<sup>9</sup> seems to think that the problem can be solved by allowing retention sutures to remain in for fifteen days.

Silk sutures have been used in 25 cases, but after using them in a case in which an infection lasted for six months I discontinued this method of closure and now use through-and-through sutures of heavy silk or of dermal suture material, which are removed on from the eighth to the tenth day. In this way no nonabsorbable material is buried in the tissue, and catgut is entirely eliminated. There is nothing original in this method of closure. The late Dr. Joseph Price used it over fifty years ago. His associate Dr. J. W. Kennedy<sup>11</sup> has continued using this method of closure, and in their combined experience they have not had a single case of dehiscence of the wound or death from infection of a wound. The reasons for not using catgut will be explained in the following paragraphs.

In view of the high percentage of cases of dehiscence of the wound, it seemed to me that there must be some other factor or factors than the explanations usually given for dehiscence, such as the type of closure, the make of catgut, infections of the wound, type of incision, respiratory infections, general debility of the patient or the choice of anesthesia. For that reason it seems logical to assume that a certain per-

11. Kennedy, J. W.: Tragedies of the Abdominal Incision, *Am. J. Surg.* 25: 512 (Sept.) 1934.

centage of patients might be considered allergic to catgut. It is only necessary to recall that one is relying on the protein of a sheep for keeping the tissues approximated.

In reviewing the case reports, the various authors do not seem to stress the fact that dehiscence of the wound in all probability is merely a more advanced stage of the same process that produces incisional hernia and causes inguinal hernia to recur after the many different methods of repair that have been advocated.

Patients were first considered allergic to catgut in 1929, after I had had 3 cases of dehiscence of the wound three weeks in succession, when no reasonable explanation could be given for this complication. I then discussed with Dr. Will Cook Spain the possibility of allergy being an explanation for dehiscence of the wound and incisional hernia. He felt that the foreign protein of a sheep introduced into a human being in certain instances would produce sufficient allergic reaction to account for the absorption of the catgut and leave the wound insecurely united.

After trying to get different makes of catgut in solution so as to try out intradermal injections of different concentrations, it occurred to Dr. Spain that we should use fresh sheep gut and in this way avoid any chemical reaction from the prepared gut. Babcock<sup>12</sup> has recently referred to allergy to catgut, but he used prepared gut and buried it beneath the skin. His reactions might possibly be due to a chemical constituent and not a true reaction to foreign protein. Dr. Spain had his technician in the "allergy clinic" at New York Post-Graduate Hospital prepare solutions of the fresh sheep gut in concentrations of 0.8 and 0.01 per cent, and these were used for the tests. After Dr. Spain gave instructions to the technician for the intradermal injections, we attempted in the "stomach clinic" of the fourth division of the Bellevue Hospital and in the wards of the fourth surgical division to determine if patients were susceptible to sheep protein. This was done on 112 patients. We aimed to take patients who had not been operated on, as we felt that the previous use of catgut might desensitize a sensitive patient or after a longer interval might make him sensitive to sheep protein. In our group of patients there were 9 who definitely showed a moderate reaction after the concentrated injection of the sheep gut.

Of the 112 cases tested, there were 103 in which the results were negative. There were 9 definite reactions with the 0.8 per cent solution in from ten to fifteen minutes after the intradermal injection. There were no reactions with the 0.01 per cent solution.

As I realized that dehiscence of the wound might possibly be due to an allergic condition, I believed that rather than try to detect the patients that were sensitive to the sheep protein, a different method of wound

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12. Babcock, W. Wayne: Catgut Allergy, *Am. J. Surg.* 27:67 (Jan.) 1935.

closure was logical. For that reason I have adopted the technic originally used by Price of using through-and-through sutures of braided silk or of dermal suture material and in this way avoid any nonabsorbable material being permanently buried in the wound. This method of closure has been used in 43 cases, and so far I have been favorably impressed by the lack of reaction from the wound.

#### SUMMARY

One should remember that there are two types of dehiscence of the wound. The first type is associated with a severe infection of the wound. In this type the disruption occurs after any method of closure. The fatalities in this series occurred in the 3 cases with severe infections of the wound associated with generalized peritonitis. The wounds in 2 of these cases were closed with through-and-through sutures. The second type of dehiscence is the one without infection of the wound, and with this type there are no other complications to account for the dehiscence. The catgut seems to be absorbed, and an allergic reaction may be the explanation for this catastrophe.

In the 19 cases in this series the dehiscence has been classified as of one of three stages. In stage 1 there is separation of the peritoneum and the posterior sheath of the rectus abdominis muscle and partial separation of the anterior sheath of the rectus abdominis muscle. It is accompanied by a moderate serosanguineous discharge. There were 4 cases of this stage of dehiscence. In stage 2 there is complete separation of all the layers of the abdominal wall, and when the sutures are removed from the skin the abdominal organs are exposed but do not protrude. There were 9 cases of this stage of dehiscence. In stage 3 there is complete separation of the abdominal wound with a protrusion of a viscus on the abdominal wall. There were 6 cases of this stage of dehiscence.

130 East Seventy-Ninth Street.

# ETHYLENE GLYCOL AND MAGNESIUM SULFATE PASTE IN TREATMENT OF INFLAMMATORY PROCESSES

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A pyogenic infection, whether fulminating or of low grade, represents one of the most common, and occasionally one of the most serious, conditions a physician is called on to treat. As is well known, the symptoms of an infection are local pain and swelling accompanied by heat and redness. The important aim of treatment is twofold: first, to prevent a spreading of the infection, and second, to relieve the symptoms. It seems worth while to describe a preparation of ethylene glycol and magnesium sulfate paste which has effected excellent results in serious as well as in trivial infections throughout a period of two years.

As the aim in treatment is to localize the infection by means of ointments or wet dressings, it would seem that a preparation of ethylene glycol and magnesium sulfate, both of which have hypertonic properties and can be kept on continuously, would assist greatly in overcoming a spreading infection or in completely aborting a less severe inflammatory process. The increase in local heat is due to hyperemia of the area under consideration. The swelling is the result of inflammatory edema. First, there is a filtering out of plasma from the blood vessels, and later the leukocytes migrate from the vessels to the involved area. Finally, red corpuscles escape passively to the outside. The pain of inflammation probably has two causative factors: distention of the sensitive tissues by the accumulating inflammatory exudate and an involvement of the nerve endings by bacterial poisons.

The plasma which filters through the capillaries soon forms a clot, since it has the same properties as the circulating plasma. The bacterial action on the cellular structures produces thromboplastin, which results in a change of the fibrinogen to fibrin, with a resulting clot, and for that reason the sooner the infection is localized the less induration there will be in the part.

Ethylene glycol is a substance that will carry magnesium sulfate as a paste, and the two chemicals have hypertonic properties. Glycerin was tried, but a paste cannot be made from it and magnesium sulfate. Certain technical difficulties are encountered in preparing an ethylene

glycol-magnesium sulfate paste; therefore, some consideration should be given to the preparation of the product. It is necessary to use approximately 60 per cent magnesium sulfate and 40 per cent ethylene glycol by volume. The exact proportion varies with the different preparations of magnesium sulfate. One should use U. S. P. magnesium sulfate manufactured by a reliable chemical house. The ethylene glycol should be brought to a boil and the magnesium sulfate slowly added to the glycol preparation and thoroughly stirred until the solution becomes adherent to the stirring rod. Then it is transferred to an electric mixer and kept in constant motion for from twenty to twenty-five minutes. A chemical change takes place when the two ingredients are mixed, which is manifested by an elevation of temperature; so the boiling of the ethylene glycol is essential in preparing the paste. One then has a thick paste, which should be allowed to stand for ten days before it is used. The preparation should be stirred daily for five minutes during this period. The paste is of a semisolid consistency and can be applied thickly over the affected area and covered by a dressing. It is usually necessary to change the paste every eight hours in cases of severe cellulitis. In cases of localized infection such as a furuncle it can be applied and the area left uncovered. The paste should be put on at frequent intervals. The object in using this preparation is to have a medicament with hypertonic properties, so that continuous osmosis will take place in the inflammatory area and by this means the infection will be localized and the edema relieved and as a result the pain greatly diminished, if not entirely overcome.

During the two year period that the preparation described has been used, more than one hundred inflammatory conditions have been observed, which have ranged from simple furuncles to severe cellulitis with lymphangitis and even to furuncles of the upper lip and around the naris. The results have been most astounding in the severe type of cellulitis. On two occasions the patient had been suffering from severe infection of the foot with extensive lymphangitis and cellulitis of the leg and had been referred for hospitalization and operation; the cellulitis in both instances subsided within five days, without surgical intervention. The preparation was first used for this type of infection, and the results have been more than gratifying.

For less severe infections the preparation has proved equally effective, and it has a definite field of application in the treatment of ordinary furunculosis or low grade infection. If the mixture is applied early in the treatment of a furuncle, it frequently aborts the process within from forty-eight to seventy-two hours, and if the condition does not subside, at least the furuncle is more quickly localized. The preparation has a wide field of application in a ward service where continuous wet

dressings are indicated, as it will diminish the amount of nursing care required in such cases.

The preparation involves little expense and requires a minimum outlay of time by both the hospital and the nursing staff. It exerts a continuous osmosis on the affected area. The preparation is definitely indicated in the treatment of pyogenic infections of the cervical lymph glands, lymphangitis and cellulitis of the extremities. Also furuncles around the upper lip and naris respond readily to the treatment.

#### COMMENT

There are three reasons for using the ethylene glycol and magnesium sulfate paste: 1. It acts more rapidly than wet compresses of magnesium sulfate or other ointments. 2. It is more uniformly successful in arresting or localizing infections than other methods of treatment. 3. It acts continuously and therefore saves nursing care.

130 East Seventy-Ninth Street.

# ARTHRITIS AND INJURIES TO JOINTS

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LOS ANGELES

The systemic phase of arthritis and rheumatic conditions has been overemphasized in recent papers, with the result that comment revolved mainly around tonsils, teeth, the gastro-intestinal tract and other possible foci of infection. Expositions have been presented of conflicting bacteriologic and serologic findings, of constitutional and endocrinologic hypotheses and, finally, of rigorous and often unbalanced diets. Little has been said about the joints, and still less is done for the joints in the management of arthritis.

A patient recently appraised the situation truthfully: "Why, you are the first doctor who ever looked at my knees! They pulled my teeth, took out my tonsils and gave me shots and diets, but they never bothered about my knees." As a result of her treatment this woman has a flexion contraction of both knees of 90 degrees and is totally crippled. With a little attention to the joints and with simple appliances this could have been prevented.

Since the pioneer work of Goldthwait the orthopedic and the industrial surgeon have not lost sight of the importance of the mechanical factor in the function of the joints. That arthritis is primarily a disease of the joints must be emphasized. Investigation, therefore, should start and center around joints. Fewer generalities and more definite knowledge of the structure, the function and the pathology of the joints is necessary in the fight against this widespread and disabling disease.

## THE EFFECTS OF DIRECT INJURY ON JOINTS

Every injury provokes a twofold effect. First, the joints suffer mechanical damage ranging from a tear in the capsule, with effusion, to detachment and laceration of cartilage or fractures of the articular surfaces. Second, the joints react to the trauma, the synovial tissue by inflammation and secretion, the bone by a resumption of the osteogenetic functions which lead to production of normal and abnormal bone. The central portion of the articular cartilage, which does not possess a blood supply, cannot react actively, but it undergoes degeneration.

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Read in part before the Industrial Accident Section of the Los Angeles County Medical Association, Nov. 8, 1934.

From the Department of Orthopedic Surgery of the College of Medical Evangelists and the Arthritis Clinic of the Cedars of Lebanon Hospital.



The first result of an effusion is distention of the capsule and increase in the intra-articular pressure. This alone is a source of irritation, as most joints are normally under negative pressure. In order to accommodate a large effusion the joint is forced into a pathologic position, which, provoking muscle spasm, limits the normal range of motion.

Recent traumatic effusions are hemorrhagic, but the blood is augmented by an increase in synovial fluid almost immediately after the injury. This intimate and direct reaction of the synovial membrane is demonstrated by examination of the joint fluid. If a hemorrhagic effusion is centrifugated, it is found that the supernatant fluid is not merely blood plasma but contains a mucinous body which gives rise to peculiar precipitative phenomena (fig. 1). If a drop of diluted acetic acid is put into the plasma, a faint cloud appears. In the joint fluid a closed membrane is formed by the precipitation of a mucin-like body.

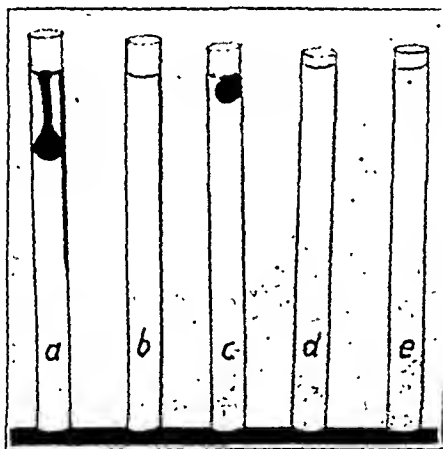


Fig. 1.—Tubes *a* and *c* show sac and tube formation in synovial fluids; tube *b*, a very thin sac in synovial fluid; tube *d*, turbidity in a pleural effusion (a positive Rivalta reaction), and tube *e*, absence of turbidity (a negative Rivalta reaction) in fluid from a serous ovarian cyst.

In extensive studies on the nature and origin of synovial fluid,<sup>1</sup> I have proved that the mucinous bodies are a secretory product and the characteristic constituent of normal and pathologic joint fluid. They were found in over 95 per cent of the traumatic effusions tested. Owing to their presence the specific viscosity of over 90 per cent of the traumatic effusions was much higher than that of blood plasma.

The irritation of a hemorrhage into the joint is therefore promptly answered by hypersecretion of the synovial fluid. If the effusion remains in the joint for a long time, permanent irritation is established with results that are clearly demonstrated in the joints of hemophiliacs.

1. Kling, David H.: *Nature and Origin of Synovial Fluid*, Arch. Surg. **23**: 543 (Oct.) 1931.

Here repeated hemorrhages occur which it is not advisable to evacuate. The synovial membrane is thickened and inflamed; the blood is broken down, and fibrin precipitates and is organized, with the formation of adhesions. The cartilage is partly degenerated by the prolonged pressure and partly eroded by an inflammatory reaction of the synovial tissue or underlying bone, which leads to irregularities of the articular surfaces and to the production of osteophytes. In short, a picture of severe arthritis with the characteristics of both atrophic arthritis and osteo-arthritis is the end-result of repeated traumatic effusion.

In severe injuries I have demonstrated the presence of fat as well as of blood in the effusions.<sup>2</sup> This fat is torn loose from the fat pads or from the bone marrow. In the former instance it indicates an injury

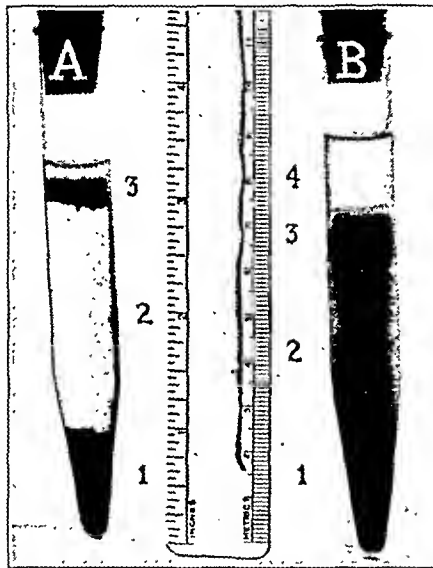


Fig. 2.—Hemorrhagic traumatic synovial fluid containing fat. *A* shows fluid with a small amount of olein centrifugated into three layers; the serum is clear. In *B* the fluid contains a large amount of olein and is separated into four layers. In both *A* and *B* the first layer is blood corpuscles; the second, serum, and the third, solid fat (palmitin and stearin). The fourth layer, in *B*, is liquid fat (olein).

to the intra-articular cartilage or to the ligaments and consists chiefly of palmitin and stearin, which are solid at room temperature. In the second case it indicates an articular fracture and consists chiefly of olein, which has a melting point of  $-4^{\circ}\text{C}$ . and is therefore liquid at room temperature. Fat in joint effusions is demonstrated simply by centrifugation. At the bottom appears a layer of blood corpuscles;

2. Kling, David H.: Fat in Traumatic Effusions of the Knee Joint, *Am. J. Surg.* 6:71 (Jan.) 1929.

above that, the plasma, and in a third layer, solid fat (fig. 2 *A*). If liquid fat is present, a fourth layer appears on top (fig. 2 *B*).

In cases of intra-articular fracture the effusions can contain also bone marrow cells.<sup>3</sup> However, the cytology of joint fluids is complicated by the presence of numerous cells, in various stages of degeneration, which may resemble bone marrow cells. A little known form of degeneration of leukocytes in effusions and various exudates consists of fragmentation and concentration of the nucleus. The leukocytes then closely resemble nucleated red cells colored with Wright's stain

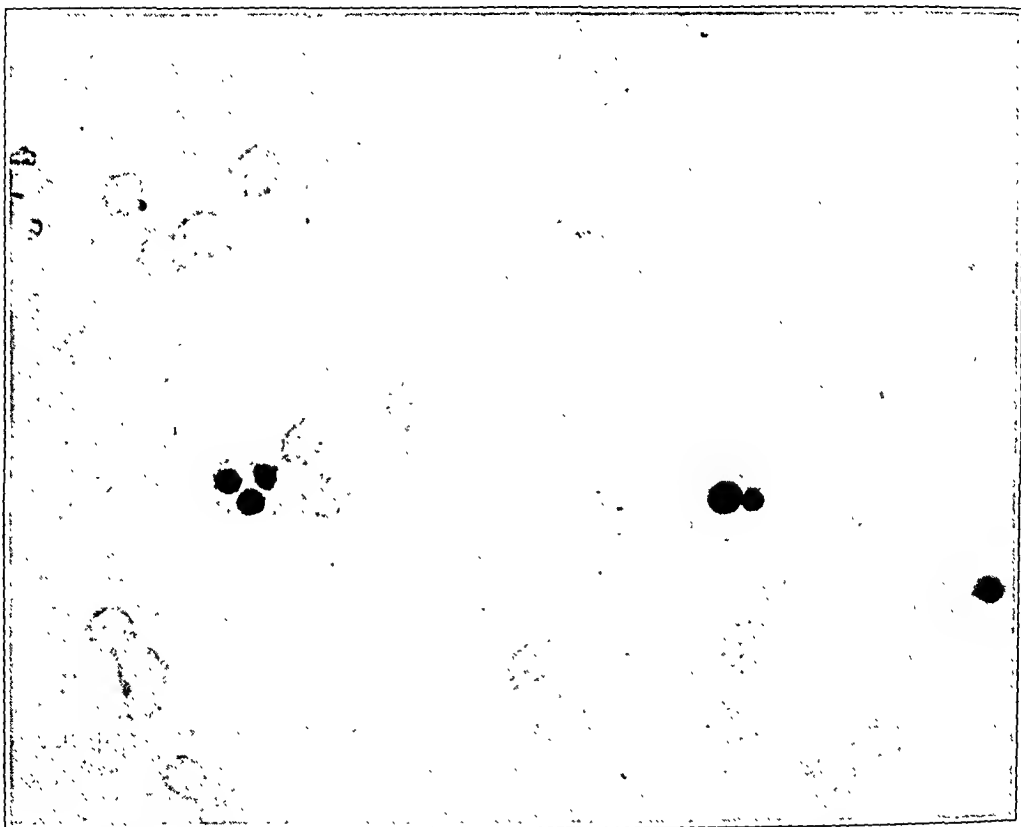


Fig. 3.—A smear from synovial fluid showing degenerated leukocytes, with fragmentation and concentration of the nucleus, resembling nucleated erythrocytes.

(fig. 3). Such degenerated leukocytes are present not only in traumatic but also in inflammatory effusions, as pointed out by Risak and Winkler<sup>4</sup> and by McEwen.<sup>5</sup>

3. Kling, David H.: Erythroblasts and Myelocytes in Traumatic Effusions of the Knee Joint, *Am. J. Surg.* **7**:824 (Dec.) 1921.

4. Risak, Eugene, and Winkler, Walter: Zur Klinik und Pathologie der Gelenksergüsse, *Deutsches Arch. f. klin. Med.* **165**:129, 1929.

5. McEwen, C.: Cytologic Studies on Rheumatic Fever: Cells of Rheumatic Exudates, *J. Clin. Investigation* **14**:190 (March) 1935.

The presence of fat in traumatic effusions distinguishes severe injuries from simple tears of the joint capsule. It further emphasizes the necessity of early aspiration of traumatic effusions. Loose bodies consisting of fibrotic fat indicate that fat precipitates and creates a chronic pathologic condition in the joint cavity which finally leads to the development of arthritis.

From the foregoing observations it follows clearly that any residue of an injury, such as particles from an effusion, a depressed condyle of a tibia, a piece of patella, a loose piece of cartilage or a torn ligament may provoke a permanent state of irritation which finally results in osteo-arthritis (figs. 4 and 5). Not only intra-articular fractures but also malunited extra-articular fractures can produce changes in the

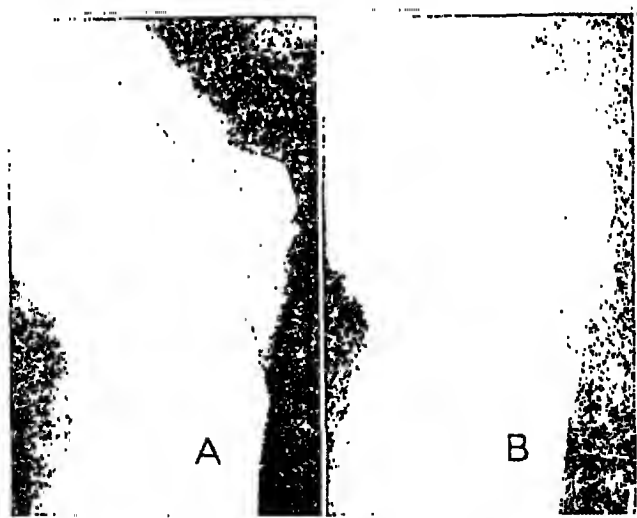


Fig. 4.—*A* shows a recent fracture of the patella, and *B*, the same patella several years later, with a spur formation at the distal end.

joints which terminate in arthritis; for instance, arthritis of the elbow may follow displacement of the head of the radius, and arthritis of the ankle or subastragaloid joints, fracture of the tibia or the os calcis. Restoration of the normal anatomic position of the fragments, therefore, is imperative in order to prevent the onset of traumatic arthritis.

For the industrial surgeon a differential diagnosis of traumatic and inflammatory joint effusions is of special interest. When the claimed injury is not recent the presence of blood cannot be a criterion because a hemorrhagic effusion could already have been absorbed. As an indicator of the source of effusion fluid I have used<sup>6</sup> the bilirubin content,

6. Kling, David H.: Bilirubin in Effusions of the Joints, *Arch. Surg.* **20**: 17 (Jan.) 1930.

which represents the end-product of a hemorrhage into the joint cavity. If, for instance, an injury occurred six weeks ago and an effusion is now present, its bilirubin content will be higher than that of blood serum. Simple methods of estimating the bilirubin content are the van den Bergh and the icteric index tests. The icteric index of traumatic effusions is above 5; that of inflammatory effusions is invariably below 5. Apart from trauma only a few conditions, e. g., hemophilia, tabetic atrophy, xanthoma or sarcoma, cause spontaneous bleeding into



Fig. 5.—Habitual dislocation of the patella, with osteochondromatosis of the intercondylar notch of the femur.

the joints and a high bilirubin content of the effusions. The special symptomatology of these rare conditions leads to the correct diagnosis.

As an illustration of the usefulness of the estimation of bilirubin I give the following abstract of a recent case:

A white man 42 years of age, accustomed to rigorous athletic exercises, e. g., sprinting, had pain and swelling of the right ankle. Roentgenograms revealed a united linear fracture of the fourth metatarsal bone, with good callus formation. The patient could not state definitely the time of fracture. He was advised by the family physician to rest as much as possible and received physical therapy of the foot. Swelling of the leg and an effusion of the right knee developed. The patient called in a second physician, who without any knowledge of the roentgeno-

grams made a diagnosis of phlebitis and infectious arthritis. He advised hospitalization and wet applications. The swelling of the leg diminished, but the effusion of the knee joint persisted. The teeth were regarded as a focus of infection, and their removal was considered. When I was called in consultation 40 cc. of slightly turbid fluid was aspirated. On examination the icteric index was 12, showing definitely that the effusion originated from a hemorrhage. This was further supported by the presence of red blood cells in the sediment, by negative cultures and by only a slight increase in the rate of sedimentation of the blood. The infectious etiology being ruled out, it was unnecessary for the patient to submit to dental surgery. With the patient resting in bed the effusion was absorbed within a week. Normal function was restored by diathermia and massage of the leg. Slight genu valgum, pronounced pronation of the feet and depression of the metatarsal arches were found and were corrected by arch supports.

The strain caused by the static imbalance of the lower extremities evidently acted as a predisposing cause of the symptomless fracture discovered by roentgenogram and of the traumatic arthritis of the knee joint.

#### THE EFFECTS OF INDIRECT INJURY ON JOINTS

The most common form of chronic arthritis is osteo-arthritis or hypertrophic arthritis. Its entire etiology is still controversial. This much, however, is certain: The first stage is degeneration of articular cartilage. Articular cartilage is very susceptible to injury even though the injury is not sufficient to be visualized in roentgenograms. It may be damaged by abnormal configuration and function of the joints as a result of previous injury or disease or of congenital malformation, such as dislocation of the hip or valgus or varus deformities of the knees and the feet. Continuous and excessive pressure and loss of normal contact are especially destructive to articular cartilage. The first step in the development of osteo-arthritis, degeneration of articular cartilage, is thus linked to trauma. The onset of symptoms is frequently traced to a trivial injury caused by a violent motion or a sprain.

The subsequent reactive manifestations, such as eburnation of the bone when it is deprived of its protecting cover of cartilage, the formation of osteophytes and the hypertrophy of synovial membrane, are at least in part induced by degeneration of the cartilage. That trauma continues to be a factor during the later stages is evidenced by clinical and pathologic features. Contrary to the current opinion that effusion is rare in osteo-arthritis, I have found periodic marked increases of synovial fluid in a large group of patients observed for a number of years. The fluids have had high viscosity and have contained a small number of cells, chiefly monocytes and synovial lining cells. This has indicated hypertrophy and hypersecretion of the synovial membrane. In about 30 per cent of the fluids I have noticed red particles which gave the chemical reaction of blood. They were therefore the precipitated remnants of small hemorrhages in the joint cavities of the patients.

The combination of constitutional anomalies with trauma in the etiology of chronic arthritis is demonstrated in Perthes' disease, habitual dislocation of the patella (fig. 5) and osteochondritis dissecans (fig. 6). The latter is of especial interest to the industrial surgeon on account of the possible development of clinical symptoms after trivial injury. I have proved that as long as the necrotic shell of bone and cartilage remains attached there is no effusion and no interference with joint function. After strain or other occupational trauma the fragment can become detached and form a loose body impinging on various parts

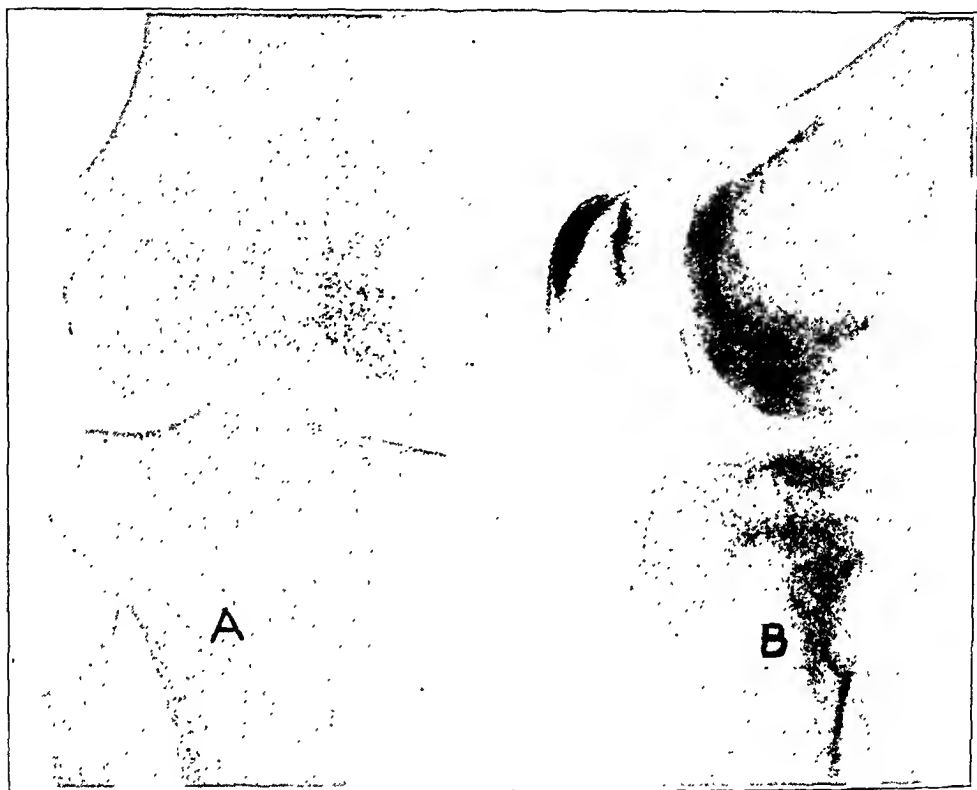


Fig. 6.—Osteochondritis dissecans of a knee joint and a loose body in the popliteal pouch. *A*, the anteroposterior view, shows the detachment of the necrotic shell beginning, and *B*, the lateral view, the loose body in the suprapatellar pouch.

of the synovial membrane, causing inflammation, effusion, limitation of motion and finally deformity of the joints.

Trauma as an etiologic factor is not confined to nonspecific arthritis. Tuberculous arthritis may be provoked by an injury. Of a group of 11 patients with syphilitic arthritis, 4 said they had had a joint injury. It has long been known and has been confirmed by recent investigations that trivial injuries may precipitate syphilitic manifestations. A positive

Wassermann reaction of the joint fluids and the blood then leads to discovery of the syphilitic infection.<sup>7</sup> Other criteria confirm the syphilitic nature of the synovitis. The following case illustrates the importance of the consideration of syphilis in traumatic surgery:

A mail carrier 39 years of age claimed that he slipped and twisted the right leg eleven days before admission to the hospital. During the next few days he noticed swelling of the knee joint, pain and limitation of motion. The diagnosis was traumatic effusion, and 40 cc. of turbid fluid was aspirated. The icteric index of the fluid was low, and blood cells were absent. This ruled out a traumatic origin of the effusion. The Wassermann reaction of the joint fluid was strongly positive. The patient refused to permit a test of the blood and said that he had not had syphilitic infection. The joint fluid was aspirated seven times in the following two months to test recurrence of the effusion. The patient then permitted a test of the blood. Only after a positive reaction was found by several laboratories did he

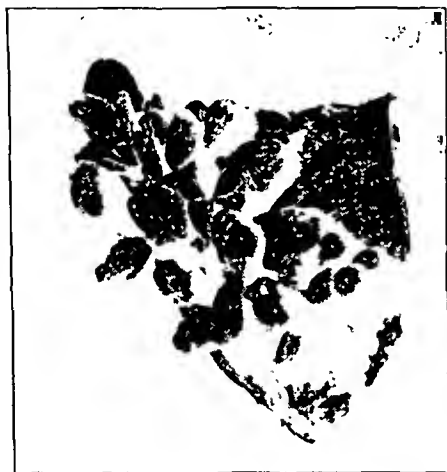


Fig. 7.—Synovial tissue in villous arthritis.

submit to antisyphilitic treatment. The effusion then disappeared, and the joint was restored to normal.

As a result of injury, chronic irritation and hypertrophy of the synovial membrane may develop and lead to the formation of villi and to persistent effusion. By examination of the joint fluid the diagnosis of villous arthritis (fig. 7) can be established.<sup>8</sup> The total number of cells is small, and in a differential count the synovial lining cells are found to constitute more than 15 per cent (fig. 8). This is an indication

7. Kling, David H.: Wassermann Reaction in Joint Fluids, *Am. J. Syph.* **13**: 596 (Oct.) 1929; Syphilitic Arthritis with Effusion, *Am. J. M. Sc.* **183**:538 (April) 1932. Kling, D. H., and Pincus, J.: Further Investigation on the Wassermann Reaction in Joint Fluid, *Am. J. Syph.* **15**:376 (July) 1931.

8. Kling, David H.: The Synovial Cells and Joint Effusions, *J. Bone & Joint Surg.* **12**:867 (Oct.) 1930.



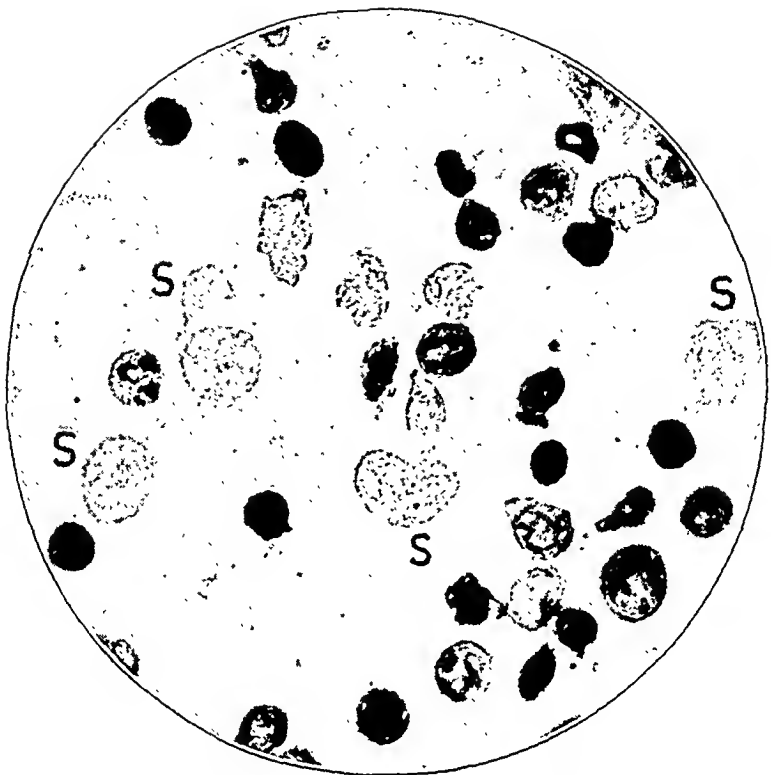


Fig. 8.—A smear from the synovial fluid of villous arthritis. *S* indicates synovial cells.

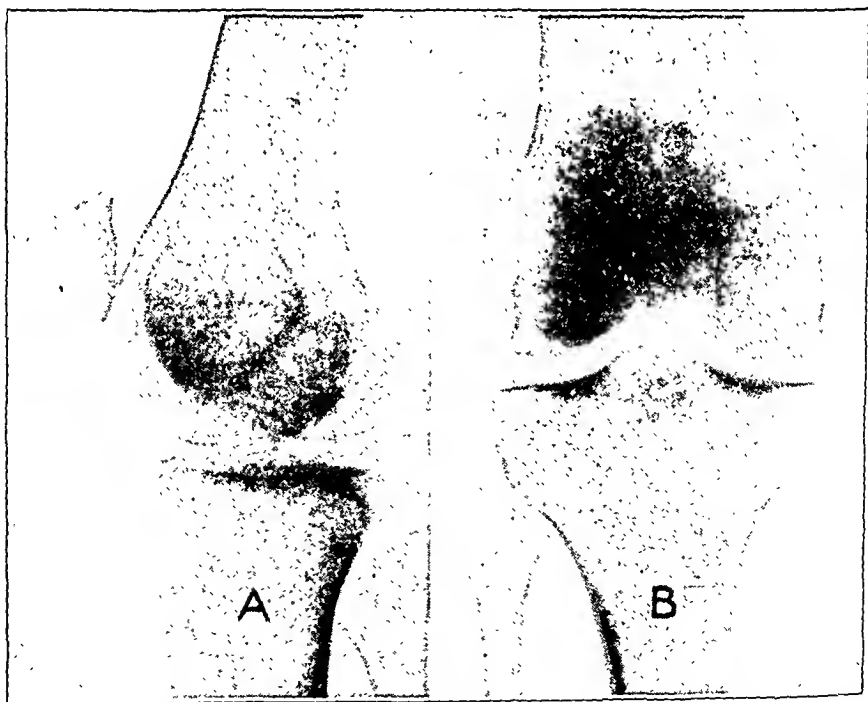


Fig. 9.—Inflation of the knee joint with air, showing hypertrophic synovial membrane in the suprapatellar pouch.

for synovectomy, which alone can restore normal conditions. Inflation of the joint with air in this and other form of synovitis is sometimes useful to visualize the configuration of the joint, the extent of the involvement and the presence of adhesions (fig. 9). The occurrence of air embolism, reported in the United States and abroad, is due to faulty technic. Before injection of air or any other gas into the joint cavity it is necessary to ascertain that no vessel has been punctured. This is done by inspection of the aspirated effusion or by injection and aspiration of a saline solution before air is introduced.

In recent years, stimulated by the extensive anatomic studies of Schmorl, surgeons began to realize the importance of injuries to the intervertebral disks and the nucleus pulposus in the development of spondylitis and other pathologic conditions of the spine. Sashin<sup>9</sup> was one of the first in this country to correlate roentgenographic evidence of herniation of the nucleus pulposus with previous trauma.

#### SUMMARY AND CONCLUSIONS

Single severe injuries to the joints as well as mild repeated trauma are important factors in the etiology of arthritis. The lesion and the irritation of the soft tissues and the bone produce inflammatory reactions which lead to hypersecretion and hypertrophy of the membrane and to deformation of the articular surfaces.

The frequent affection of articular cartilage by trauma leads to degeneration and erosion and may provoke the development of osteoarthritis. Trauma not only presents the first link in the chain of pathologic changes in unspecific osteo-arthritis but may open a path for the invasion of the joint by nonspecific organisms as well as by the tubercle bacillus and *Spirochaeta pallida*.

The examination of joint effusions is an important means of determination of the severity of an injury and of differentiation between traumatic and inflammatory effusions and between specific and nonspecific conditions of joints. The aspiration of the joint evacuates pathologic products from the joint cavity and reduces irritation and thus promotes the restoration of normal conditions.

Requirements for the prevention of arthritis after injuries of joints or in the vicinity of joints are reduction of fractures, early removal of loose or lacerated cartilage and repair of ligaments. Proper therapy, with rest, fixation of the fracture and resumption of motion, is of the utmost importance; it requires thorough understanding of the physiology and pathology of joints, and great clinical experience. The early recognition of constitutional or acquired anomalies and diseases which

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9. Sashin, David: Intervertebral Disk Extensions into the Vertebral Bodies and Spinal Canal, *Arch. Surg.* **22**:527 (April) 1931.

are apt to traumatize or invade the joints, such as osteochondritis dissecans, Perthes' disease, genu valgum and genu varum, syphilis, tuberculosis and endocrine disturbances, opens a way for preventive measures to reduce the development of chronic arthritis.

My plea to restore to the joint priority in the consideration of the problems of arthritis is intended not to minimize extra-articular factors but to furnish a firm groundwork of controlled facts, which alone assures steady progress in the recognition and therapy of disease.

1930 Wilshire Boulevard.

# EFFECTS OF CIRCULATORY DISTURBANCES ON THE STRUCTURE AND HEALING OF BONE

INJURIES OF THE HEAD OF THE FEMUR IN YOUNG RABBITS

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BOSTON

Adequate nutrition is essential for the normal structure and function of bone tissues and for repair after injury. The anatomic relations of joints and their articular cartilage, the growth of bone in the metaphyses and the repair of fractures and dislocations are specific problems of the skeletal system in which nutrition is a determining factor. Studies of diseases and injuries of bone and their repair demand a knowledge of the intrinsic vascular pattern and of the opportunity for collateral circulation of most bones and, in particular, of certain bones and epiphyses.

Many reports, some speculative and conflicting, have included a discussion of the etiology and repair of various forms of osteochondritis, aseptic and septic necrosis, epiphyseal slipping or separation and other more or less obscure changes in the epiphyses and in their cartilage. There is, further, some doubt regarding the normal circulation of bone and the importance of the various sources of blood and collateral circulation. Many investigators have expressed the opinion that trauma is important in producing changes in bone; others have concluded that trauma, except in fractures and dislocations, affects bone only by mechanical distortion of a primary osseous defect. The latter theory presupposes a vascular disturbance, with or without a mild infectious agent, but it is confronted by discordant statements concerning the vascular pattern of bone.

In a recent experimental study<sup>1</sup> infarcts were produced in the femur in rabbits by injecting a suspension of particulate charcoal into the principal nutrient artery of the shaft. The changes produced were correlated with a review of the clinical disorders in human tissues and with experimental studies concerned with aseptic necrosis in bone and the blood supply of these tissues. Further studies<sup>2</sup> demonstrated that

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From the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago, John Jay Borland Fellowship for Clinical Research, and the University of Alabama Medical School, University, Ala.

1. Kistler, G. H.: Sequences of Experimental Infarction of the Femur in Rabbits, *Arch. Surg.* **29**:589 (Oct.) 1934.

2. Kistler, G. H.: *Surg., Gynec. & Obst.* **60**:913, 1935.

agglutinated staphylococci act as emboli and, when living, infect the infarcted tissues. The infarcts produced occurred regularly beneath epiphyseal and other cartilage, tissues that are vulnerable because of a peculiar capillary blood supply and an inadequate collateral circulation. No noteworthy vascular connection between the epiphyses and the diaphysis of the femur was present in these growing rabbits. In the small septic infarcts, clumps of staphylococci were noted in the lacunar spaces between columns of calcified matrix projecting into ossifying epiphyseal plates and other cartilage. The suggestion was made then that embolic occlusions of end-capillaries beneath epiphyseal plate cartilage cause infarcts in the shaft of the femur and beneath articular cartilage cause subchondral lesions, such as tuberculosis or other infections in the epiphyses, even when the epiphyseal plate cartilage has disappeared and longitudinal growth has ceased.

The head of the femur is often the site of infection, injury and necrosis with or without clearly associated trauma. The changes are those which occur in epiphyses generally and those associated with weight bearing and the particular anatomic structure of the head and neck of the femur. These are often attributed to a vascular disturbance of the epiphysis with consequent damage of the tissues and some deformity of the part by mechanical stress. The capital epiphysis especially is subject to vascular disturbances. The opportunity for the development of collateral circulation here is limited. The entire head is intracapsular, being covered by articular cartilage; the only sources of blood supply are through the ligamentum teres femoris, through the epiphyseal vessels from the periosteal attachment of the capsule at the margin of the head and, in the adult femur, through the vessels of the shaft. Disturbances within the head of a growing femur are distinct from and should not be confused with those of the metaphysis of the shaft or isolated lesions of the epiphyseal cartilage plate.

The damage to osteoid tissue by an injury of the blood supply of the head of the femur and the subsequent repair depend on the importance to normal nutrition of the interrupted blood supply, on the opportunity to obtain collateral circulation and on the presence within the head of anastomoses from the three possible sources of blood. Lexer,<sup>3</sup> Chandler and Kreuscher<sup>4</sup> and many others, by injection experiments and histologic examination, demonstrated the entrance of vessels into the head of the femur through the round ligament which they said were important. Nussbaum<sup>5</sup> and Walmsley<sup>6</sup> refuted the presence of these

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3. Lexer, E.: *Arch. f. klin. Chir.* **71**:1, 1903.

4. Chandler, S. B., and Kreuscher, P. H.: *J. Bone & Joint Surg.* **14**:834, 1932.

5. Nussbaum, A.: *Beitr. z. klin. Chir.* **130**:495, 1924.

6. Walmsley, T.: *J. Anat. & Physiol.* **49**:434, 1915.

vessels. Zemansky and Lippmann<sup>7</sup> produced marked changes and coxa vara deformity of the head of the femur in rabbits 2 weeks of age, but not in adults, by cutting the ligamentum teres. After producing such a lesion in young goats, Graham<sup>8</sup> noted moderate changes indicating a nutritional disturbance. These alterations were not typical of the osteochondritis described by Legg,<sup>9</sup> Perthes<sup>10</sup> and Calvé.<sup>11</sup> Stewart<sup>12</sup> could not regularly produce aseptic necrosis in rabbits and dogs by cutting the round ligament and circumcising the periosteum of the neck of the femur. He said that he considered that the blood supply from the neck is usually sufficient to preserve the vitality of the head, and he made no distinction between growing and adult femurs. The presence of a vascular communication is implied between the diaphysis and its epiphyses through the conjugal cartilage plates. Miltner and Hu<sup>13</sup> produced necrosis of the head by stripping the periosteum of the neck and ligating the neck and the round ligament. Internal weakening and weight bearing resulted in collapse of the epiphysis, lesions they considered comparable to osteochondritis of the head.

Many clinical studies have been published of intracapsular fracture of the femur. Santos,<sup>14</sup> Freund,<sup>15</sup> Speed,<sup>16</sup> Wolcott<sup>17</sup> and others have emphasized the importance of the ligamentum teres in repair and in preventing necrosis and deformity of the fractured segment. Camitz<sup>18</sup> stated that the round ligament alone may prevent necrosis of the proximal fragment. These investigators stated also that the absence of a capsular attachment is a serious handicap to healing and that injury to the capsule and round ligament by dislocation may cause nutritional disturbances of the head. Walmsley studied the head of the femur after the postmortem injection of a dye into the bodies of two boys, 2 and 6 years of age. Some dye was distributed to the tissues of the head

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7. Zemansky, A. P., Jr., and Lippmann, R. K.: *Surg., Gynec. & Obst.* **48**: 461, 1929.

8. Graham, R. V.: *M. J. Australia* **1**:207, 1930.

9. Legg, A.: *Arch. franco-belges de chir.* **25**:585, 1922.

10. Perthes, G.: *Klin. Wchnschr.* **3**:513, 1924.

11. Calvé, J.: *Arch. franco-belges de chir.* **25**:592, 1922.

12. Stewart, W. J.: *J. Bone & Joint Surg.* **15**:413, 1933.

13. Miltner, L. J., and Hu, C. H.: Osteochondritis of the Head of the Femur, *Arch. Surg.* **27**:645 (Oct.) 1933.

14. Santos, J. V.: Changes in the Head of the Femur After Complete Intracapsular Fracture of the Neck, *Arch. Surg.* **21**:470 (Sept.) 1930.

15. Freund, E.: *Virchows Arch. f. path. Anat.* **261**:287, 1926.

16. Speed, K.: *Ann. Surg.* **96**:951, 1932.

17. Wolcott, W. E.: Circulation of the Head and Neck of the Femur: Its Relation to Nonunion in Fractures of the Femoral Neck, *J. A. M. A.* **100**:27 (Jan. 7) 1933.

18. Camitz, H.: *Acta chir. Scandinav. (supp. 19)* **68**:1, 1931.

through the vessels of the capsule and the periosteum but none through those of the round ligament. The importance of the blood supply to the head of the femur from the joint capsule was emphasized by Harris,<sup>19</sup> who injected dye into a puppy and into a human fetus. Bentzon<sup>20</sup> injected alcohol about the arteries of the upper epiphysis of the femur in young rabbits and produced a coxa plana deformity. He attributed this result to trauma and blocking of adventitial nerves, with active hyperemia of the head. Stewart observed that circumcission of the periosteum of the neck in rabbits and dogs added no appreciable circulatory disturbance when the round ligament had been cut. Miltner and Hu, however, ligated the neck after stripping off the periosteum, and they demonstrated a greater necrosis of the head when the round ligament was ligated than when it was intact.

There is some uncertainty whether or not the epiphyseal cartilage plate of a growing bone is a barrier to nutrition of the head from the circulation of the shaft. Embolic infarcts, produced experimentally in rabbits, occurred chiefly in the metaphyses beneath cartilage plates, where focal necrosis of bone frequently is present clinically. The adjacent epiphyses were not affected except by direct extension with septic emboli. Both septic and aseptic necrosis within the metaphysis included a definite portion of the growing cartilage plate. Epiphyseal separations occurred along a plane between the necrotic ossifying and the proliferating cartilage tissues where the metaphyseal end-capillaries did not anastomose with the epiphyseal circulation. Charcoal emboli distributed to the vessels of the capsule of the hip joint and the ligamentum teres in young rabbits produced marked necrosis of the tissues of the head, as though no appreciable blood supply were derived from the shaft. Occasionally, however, collateral circulation for repair of the head developed from the shaft through the cartilage plate. Kolodny<sup>21</sup> and Eliason and Ferguson<sup>22</sup> gave as their opinion that a few vessels enter the head from the tissues of the shaft but that they have less importance than the periosteal blood supply which enters the margin of the articular cartilage. Stewart concluded that the vitality of the tissues of the head can be maintained by the circulation in the neck, presumably in a growing as well as in an adult femur.

The existence of end-capillaries in the epiphyses, such as those in the growth centers of the shaft, also has been studied. Phemister,<sup>23</sup> extending the work of Santos, reported clinical and pathologic studies of dislocation and intracapsular fractures of the head of the femur

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19. Harris, H. A.: *J. Anat.* **64**:3, 1929.

20. Bentzon, P. G. K.: *Brit. J. Radiol.* **31**:439, 1926.

21. Kolodny, A.: *J. Bone & Joint Surg.* **7**:575, 1925.

22. Eliason, E. L., and Ferguson, L. K.: *Surg., Gynec. & Obst.* **58**:85, 1934.

23. Phemister, D. B.: *Surg., Gynec. & Obst.* **59**:415, 1934.

and stressed the need of an adequate blood supply to avoid necrosis and to promote union of a separated fragment. He stated that he had observed little evidence of epiphyseal end-capillaries like those thought to be present in the metaphyses. When septic emboli were directed into the head and great trochanter of the femur, focal subchondral regions of necrosis appeared. These began minutely in the lacunar spaces between columns of calcified cartilage similar to those of the metaphyses following embolic infarction through the principal nutrient artery of the shaft.

Expansile growth of the epiphyses is similar to growth in length in the metaphyses. The latter, possibly, is more rapid because of the abundant blood supply to the proliferating plate cartilage from the epiphysis, as compared with the relatively poor nutrition of articular or other cartilage about the epiphyses. Where growth is active the end-capillaries are long and numerous, conditions favoring the more frequent occurrence clinically of foci of necrosis in some growth regions than in others. A wide metaphysis is considered more vulnerable than a narrow one, because in the wide metaphysis the center is farther from collateral periosteal blood supply. Some expansile growth may continue in an epiphysis after it has united with the diaphysis, thus providing end-capillaries and the possibility of subchondral foci of septic or aseptic necrosis in an otherwise adult bone.

The destruction of an artery to a bone does not duplicate embolism of its branches or end-capillaries within the bone. The large vessels of the medullary tissues may become channels for collateral circulation from another external source. Therefore, a few small emboli may produce greater injury to osteoid tissue than severe trauma.

#### EXPERIMENTAL METHODS

Experiments were designed to study the normal blood supply and vascular pattern of the head of the growing femur in rabbits and the relative importance of the various sources of blood in maintaining nutrition for normal growth and the repair of injuries. Various operative procedures were performed especially to determine the importance of the ligamentum teres and the capsule of the hip joint as sources of blood to the head in the repair of intracapsular fractures.

The following experiments were performed on one hundred and sixty-six rabbits ranging in age from 12 hours to 35 days: (1) ligation or evulsion of the principal nutrient artery to the shaft, (2) interruption of the vessel that passes through the trochanteric notch, (3) division of the ligamentum teres, (4) division of the ligamentum teres and interruption of the vessels that pass through the trochanteric notch, (5) division of the ligamentum teres and ligation or evulsion of the principal nutrient artery to the shaft, (7) ligation of the neck of the femur with black silk, (8) division of the ligamentum teres and ligation of the neck of



the femur with black silk, (9) fracture of the head of the femur and (10) division of the ligamentum teres and fracture of the head of the femur.

The rabbits were fed stock rations of oats, green vegetables and hay. Each group contained animals of two ages: from 12 hours to 5 days old and about 30 days old. The operations were performed with aseptic precaution with the animals under phenobarbital sodium anesthesia; very young animals required no anesthetic. The principal nutrient artery to the shaft was exposed through an incision on the anterior surface of the upper third of the thigh. It was isolated near its origin from the lateral circumflex artery and was identified by dissection down to the nutrient foramen, where it was ligated or evulsed outside the cortex of the shaft. Access to the structures within the hip joint was obtained through a similar incision in the thigh with the leg abducted and rotated outward. In some earlier experiments the joint space was opened from above, but was unsatisfactory as the head was not exposed properly and dislocation sometimes occurred later through the opening in the joint capsule. The branch of the deep femoral artery which enters the proximal end of the shaft through the trochanteric notch was isolated and interrupted through an incision laterally over the great trochanter.

The operation usually was performed on the right femur, the left serving as a control. The animal was killed from a few hours to seventy-six days after operation; the femurs were fixed in Klotz' solution no. 1, containing solution of formaldehyde U. S. P. in a concentration of 10 per cent. The bone tissues were decalcified in 4 per cent nitric acid and cut transversely into three segments and, then longitudinally into blocks, the number varying with the size of the femur. Blocks of the proximal portions of the femurs, many acetabula and the middle and distal portions of the femurs, when indicated, were then embedded in pyroxylin and paraffin. Many sections at various levels were cut and stained with hematoxylin and eosin. Other sections from animals which had been given intravenous injections of lithium carmine or india ink were examined, stained and unstained.

### RESULTS

After operation some of the rabbits showed disability of the leg, the degree depending on the kind of experiment performed and the subsequent changes in the head of the femur. No attempt was made to immobilize the affected leg. Interference with the principal nutrient artery to the shaft, with the vessel that passes through the trochanteric notch or with the ligamentum teres produced no disability or slight disturbance of the leg for about two days. After the more extensive procedures with greater trauma to the soft tissues, the leg was held partially flexed at the hip and knee for a few days; then it was used like the control leg. The leg often was rotated internally at the hip, and the lower portion of the leg and the foot were extended outward from the body, owing to downward flattening and anterior rotation of the head of the femur. Frequently the leg operated on was shorter than the control leg, owing to downward displacement of the head of the femur on the neck or to hypoplasia of the neck itself. The greatest disability occurred when the head separated from the neck or after fracture without permanent fixation of the isolated segment (pseudarthrosis). Even when this took place the rabbit moved about within from six to ten days after operation without favoring the affected extremity and had no noteworthy deformity except a variable degree of shortening and corresponding prominence of the great trochanter. The extent of passive motion of the leg was diminished by fibrous thickening of the joint capsule. In the joints usually one cartilage surface, epiphyseal plate or newly formed cartilage about it was opposite the acetabulum, which had been remolded to fit the contour of the new articulating surface of the femur.

The neck of the femur in some instances was small, and the degree of hypoplasia was proportional to the extent of injury to the head, but it was most marked in young animals. The diameter of the proximal end of the femur was smaller than that of the control bone, owing to diminished growth in the metaphysis of the head. The length of the femur measured from the root of the neck often was less than that in the control, although the total lengths of the bones were the same. Histologic preparations also demonstrated that the portion of the proximal metaphysis of the shaft forming the great trochanter had grown away from the neck.

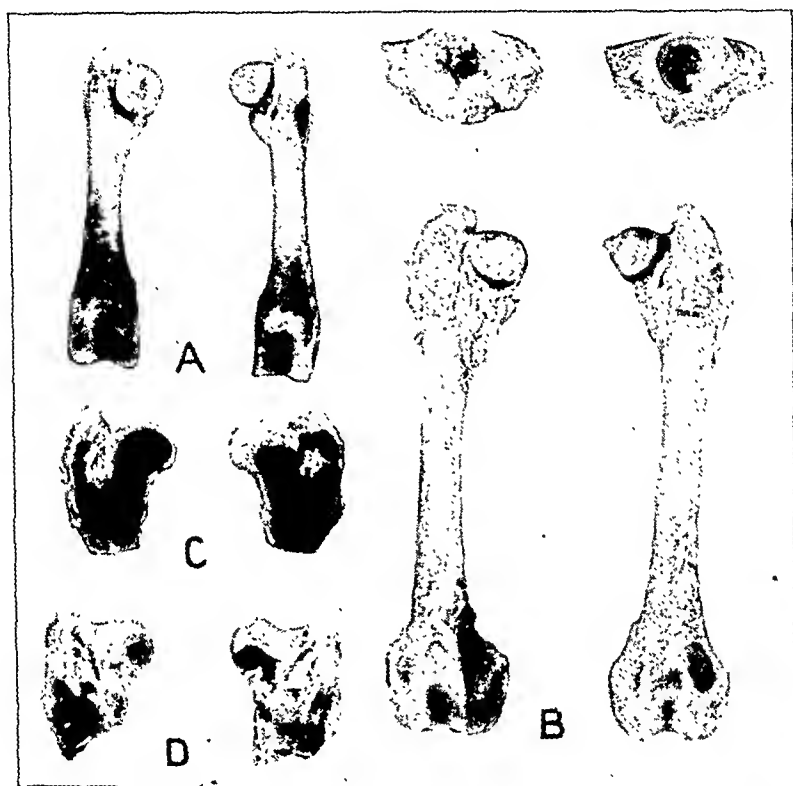


Fig. 1.—The femurs of rabbits after division of the right ligamentum teres. *A*, downward and anterior displacement of the head of the right femur twenty-one days after operation, performed when the animal was 4 days old. The principal nutrient artery to the shaft also was interrupted. *B*, the head and the acetabulum of the right femur are larger than those of the left, and the head is broad (forty-nine days after operation, performed when the animal was 11 days old). *C*, marked temporary interference with the blood supply to the head of the right femur four days after operation, performed when the animal was 21 days old (surfaces made by cutting after decalcification). *D*, periosteal collateral circulation to the head of the right femur seventy days after operation, performed when the animal was 10 days old.

*Ligation or Evulsion of the Principal Nutrient Artery to the Shaft.*—The only significant changes in the femur occurred in rabbits a few days old. Because of diminished ossification in the proximal metaphysis, the epiphyseal cartilage tissue

of the head was slightly wider than that of the control a few days after operation. Tissue from the heads of the femurs that had been operated on contained as much india ink or lithium carmine as that from the controls after intravenous injections had been given.

*Interruption of the Vessel That Passes Through the Trochanteric Notch.*—No noteworthy changes occurred in the head of the femur when this branch of the deep femoral artery was ligated or evulsed. Changes suggesting a slight nutritional disturbance occasionally were noted in the proximal metaphysis of the shaft. They were more marked in the metaphysis when both the vessel that

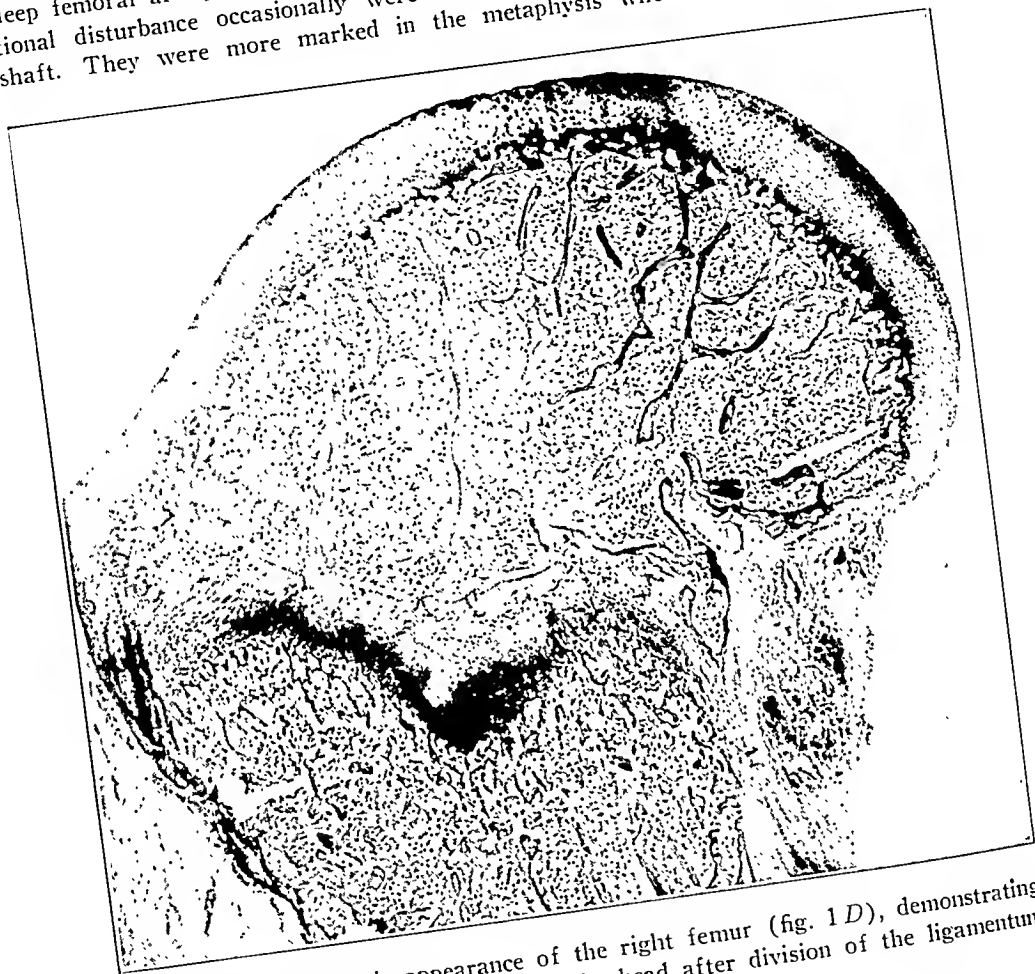


Fig. 2.—Microscopic appearance of the right femur (fig. 1 D), demonstrating the periosteal collateral circulation to the head after division of the ligamentum teres.

passes through the notch and the principal nutrient artery to the shaft were interrupted, but even these procedures caused no disturbance in the head of the femur.

*Division of the Ligamentum Teres.*—In young growing rabbits division of the ligamentum teres produced fairly uniform gross structural changes, most marked from ten to twenty days after operation (figs. 1 and 2). The head of the femur was broader and flatter, so that the margin overhung the neck and the stump of the ligament was depressed. The corresponding acetabulum was wider and shallower so as to accommodate the head, the articular surface being as much

as 60 per cent larger than that of the control. A slight to moderate anterior rotation of the head turned the shaft inward; occasionally the neck was short, because of a decreased proliferation of cartilage in the epiphyseal plate and a consequent diminution in growth. At the margin where the joint capsule is attached to the head the tissues were hyperemic, especially in the medial and posterior portions. There were no noteworthy alterations of the head in a few adult rabbits. In two of the twenty-five rabbits in this series, ranging in age from 12 hours to maturity, the head of the femur separated from the neck at the epiphyseal line and liquefied within the joint space. These femurs may have been infected. When india ink or lithium carmine was injected intravenously into growing rabbits, less material was present in the head in animals in which the round ligament had been cut than in the controls.

The microscopic changes in the head when there was no ligamentous attachment were essentially those usually caused by a mild nutritional disturbance and were mainly located about the fovea centralis. The amount of spongy bone decreased and that of osteoid tissue increased in the ossification centers in rabbits a few days of age; the fibrillar stroma of the medullary tissues was denser, and the number of cellular elements was diminished. There were a few small foci of necrosis. Sometimes the epiphyseal cartilage was narrowed because of a diminished proliferation of cartilage, and the vessels to the capsule entering the periphery of the head, where the articular and the epiphyseal cartilage unite, were dilated for collateral circulation. No collateral circulation developed from the tissues of the diaphysis through the cartilage plate. Marked necrosis in the tissues of the head was present after the ligamentum teres had been cut and a suspension of particulate charcoal had been injected through the deep femoral artery, which is the main blood supply to the tissues about the neck of the femur in the rabbit. The normal femur of a fetus or rabbit up to a few days of age had small vessels in the cartilage of the head which passed upward from the margin of the epiphysis and downward from the fovea toward the region where the secondary ossifying center forms or to the small center already present.

*Division of the Ligamentum Teres and Interruption of the Vessel That Passes Through the Trochanteric Notch; Division of the Ligamentum Teres and Ligation or Evulsion of the Principal Nutrient Artery to the Shaft, and Division of the Ligamentum Teres, Interruption of the Vessel That Passes Through the Trochanteric Notch and Ligation or Evulsion of the Principal Nutrient Artery to the Shaft.*—The changes in the head of the femur resembled those caused by cutting the ligament. They occurred only in growing rabbits, the extent of the alteration being inversely proportional to the age of the animal. The epiphyseal cartilage of the head was not widened, as it was when the principal artery to the shaft and the trochanteric vessel were destroyed but the ligamentum teres was left intact. This indicates that the blood supply to the ligamentum teres is important for proliferation of cartilage in the proximal epiphysis.

*Ligation (Black Silk) of the Neck of the Femur* (figs. 3 and 4).—Rabbits 30 days old had no gross deformity of the head of the femur after intracapsular ligation of the neck. The round ligament was large, and the haversian gland tissue of the acetabulum was hyperemic. Vascular granulation tissue covered the silk ligature. A moderate amount of fibrous tissue replaced the marrow, especially in the periphery; the amount of osteoid tissue was increased, in some instances spicules being parallel to the articulating surface, like a line of arrested growth. The attachment of the ligamentum teres contained many vessels larger than those of the control femur. Enlarged vessels also entered the head from the vascular tissues formed about the neck at its junction with the head.

Black silk tied about the neck of the femur of rabbits about 4 days of age usually produced complete necrosis and separation of the head. The separated head of one of these, examined thirty-four days after operation, was attached to the ligamentum teres, which protruded from a small and narrow acetabulum. This head, smaller than that of the control femur, contained a definite ossification center.

*Division of the Ligamentum Teres and Ligation (Black Silk) of the Neck of the Femur* (figs. 5 to 7).—The ligamentum teres was cut, and one or more loops



Fig. 3.—Partial necrosis, showing the line of arrested growth and fibrous tissue reaction in the head of the femur ( $\times 16$ ) thirty-six days after intracapsular ligation of the neck, performed when the animal was 31 days old. Many large blood vessels enter the head from the ligamentum teres and the vascular periosteal granulation tissue but none from the marrow of the shaft through the epiphyseal plate.

of silk were tied tightly about the neck of the femur inside the capsule and close under the peripheral edge of the proximal epiphysis. Changes in the head in growing rabbits in this group were considerably more marked than those following one or the other operative manipulation alone. In three of the eight animals

the head separated entirely from the neck of the femur through the epiphyseal line and partially or completely liquefied inside the joint capsule. The rabbits in which this occurred were 1½, 4 and 31 days old at the time of operation. The remaining five, from 12 hours to 34 days old, showed marked changes, consisting of decreased growth of the head, downward and forward displacement of the head, hypoplasia of the neck and marked proliferation of vascular granulation tissue from the neck to the lip of the head over the black silk ligature. The ligature on two femurs later was found to be loose, so that the periosteal blood supply to the head probably had not been stopped. The total length of the femurs

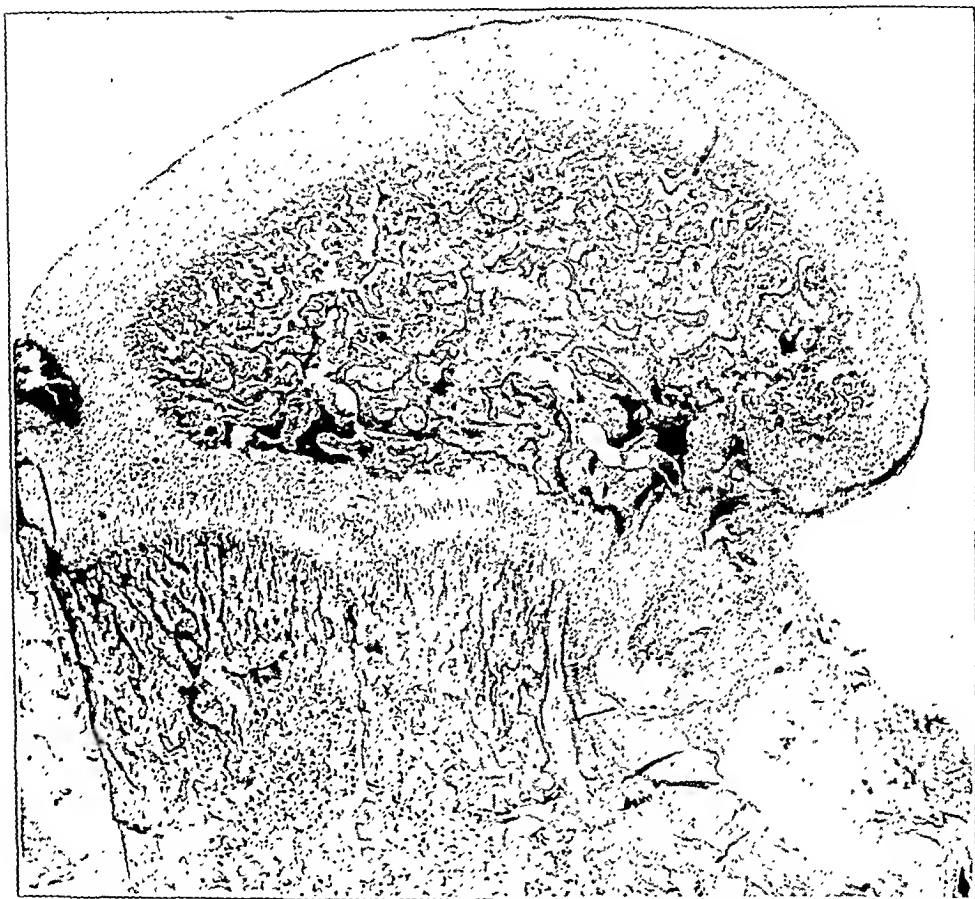


Fig. 4.—A section at a different level of the head shown in figure 3, illustrating revascularization from the collateral periosteal tissue that spans the space formerly occupied by the silk ligature.

that had been operated on equaled that of the controls, but the length below the base of the neck was less than that of the controls because of hypoplasia in the growth center of the metaphysis of the neck.

The head of the femur of one rabbit, operated on twelve hours after birth and examined thirty-five days later, was small and flat and was rotated about 60 degrees anteriorly on the shaft. It had no neck and was about 1 cm. below the base of the great trochanter. A shallow and narrow acetabulum articulated with the deformed head. The development of the acetabulum in these experiments seemed to depend on the size, growth, shape and contour of the articulating head.

The tissues of the head were necrotic, and in the animals that lived longest they were replaced by a creeping substitution of tissues from the periphery of the head, where collateral circulation had developed over the silk ligature about the neck. The necrosis included the epiphyseal cartilage, especially the center, but usually not the articular cartilage except the deeper portions. When separation of the epiphysis occurred, the narrow portion of cartilage plate adjacent to the region of growth in the metaphysis remained attached to the neck. The remaining portion of the plate separated with the head. The granulation tissue covering the silk ligature occasionally contained new periosteal bone and many blood vessels, which entered the shelving edge of the head. No noteworthy collateral circulation developed from the metaphysis through the cartilage plate to the head.

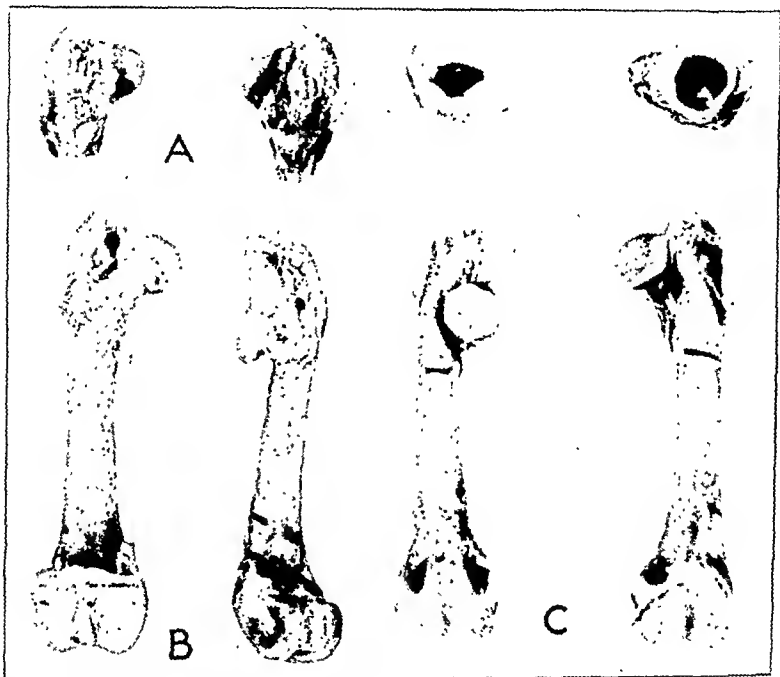


Fig. 5.—The femurs of rabbits after division of the right ligamentum teres and ligation of the neck. *A*, hypoplasia of the head and neck of the right femur with periosteal tissue for collateral blood supply to the head thirty-six days after operation, performed when the animal was 31 days old. *B* and *C*, marked hypoplasia of the head, neck and acetabulum and anterior rotation of the head, thirty-five days after operation, performed when the animal was 12 hours old.

*Fracture of the Head of the Femur* (figs. 8 to 10).—The head of the femur was cut from the neck and then fastened with a metal pin in its original position. In small animals the head was separated from the neck but not splinted. Owing to irregularities in the plane of the epiphyseal line, a portion of the head usually remained attached to the neck; sometimes parts of the epiphyseal line and tissues of the metaphysis were included with the fractured segment. When the head was held by a metal pin, it united quickly and firmly with the neck, and fifteen days after the operation only a linear scar remained at the fracture, surrounded

by a narrow zone of fibrous tissue. There was only slight deformity of the head, due to inaccurate alinement of the fractured segment. The size of the ossification center of the head was similar to that of the control femur, and the head occasionally contained fibrous tissue, indicating the presence of nutritional disturbance. In two cases union did not occur because fixation of the severed fragment was unsuccessful, but the head was as large as that of the control femur and consisted of normal tissue. Fixation by pin probably was insufficient to withstand the stress of weight bearing. The round ligament was larger and more hyperemic than that of the control, and the haversian gland of the acetabulum had more vascular fat tissue.



Fig. 6.—The head of the right femur ( $\times 16$ ) shown in figure 5 *A*. Necrosis of the tissues is marked, and the small ossification center has a wide layer of articular cartilage and osteoid tissue. No blood vessels enter the head from the metaphysis of the short neck.

When the fracture of the head was sufficiently far above the epiphyseal line to leave an intact layer of epiphyseal tissue, there was partial necrosis, and healing was delayed, particularly in the central portion, owing to the distance from periosteal blood supply and to the absence of collateral circulation through the cartilage plate from the shaft. Occasionally a portion of the neck and the epiphyseal cartilage plate was included in the segment. In these cases the tissues of the



neck and the metaphyseal margin of the cartilage plate became necrotic; the body of the cartilage plate receiving its blood from the head remained viable, as well as the tissues of the epiphysis.



Fig. 7.—The proximal end of the right femur ( $\times 10$ ) shown in figure 5 *B* and *C*. The flat cartilage has a small ossification center, and the epiphyseal line is parallel to the shaft and perpendicular to the line beneath the great trochanter, owing to the usual growth of the shaft from the great trochanter.

When the head was fractured but was not fixed to the femur (rabbits from 12 hours to 5 days of age), it did not unite with the neck. The femur grew

more rapidly than did the control and occasionally contained small regions of necrosis. The ossifying center, however, was smaller, and the articular cartilage was much wider than in the control femur. The symmetry of the head was maintained, the articular surface was smooth, and the broken surface, even though made through a small ossification center, usually became covered by a narrow, smooth layer of hyaline cartilage. The growth of the small acetabulum was not commensurate with that of the ununited head, and the acetabulum remained as a little shallow depression from which the head was forced into the joint space by its own growth. Marked hyperemia and an increase in the amount of fibrous connective tissue of the ligamentum teres and haversian gland tissue were noted.

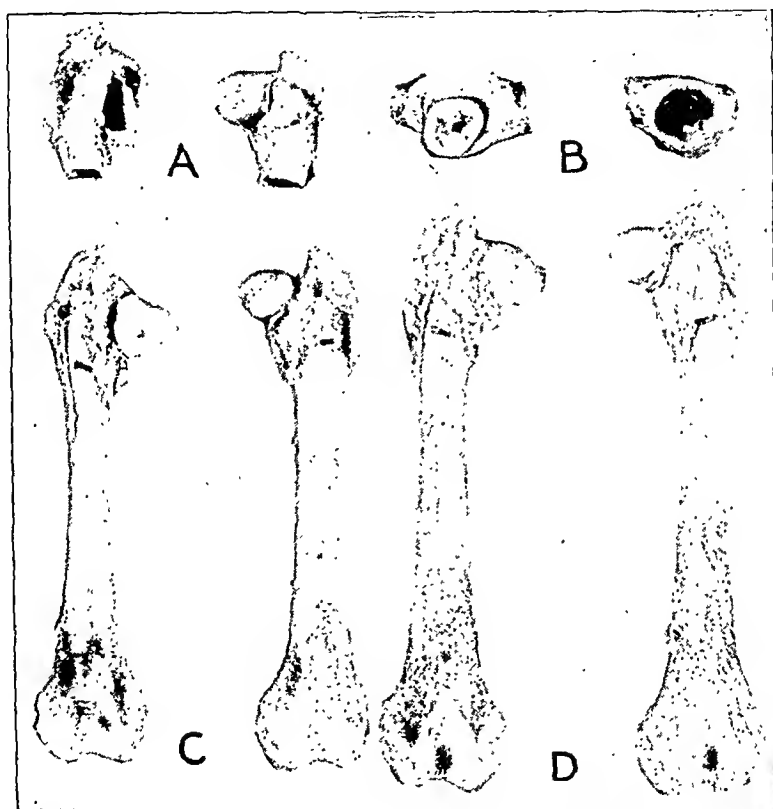


Fig. 8.—The head of the right femur was fractured inside the capsule of the hip joint, and in *C* and *D* it was splinted by metal pins. *A* and *B*, nonunion of the head thirty-five days after operation, performed when the animal was 12 hours old. The head developed as usual when attached only by the ligamentum teres, but the acetabulum remained narrow and shallow. *C* and *D*, firm union of the head of the right femur forty-five days after operation, performed when the animal was 30 days old. The round ligament is large and vascular.

*Division of the Ligamentum Teres and Fracture of the Head of the Femur* (figs. 11 and 12).—In these experiments the ligamentum teres was cut, and the head was fractured and, where possible, was splinted with a pin. The ligamentum teres was large, hyperemic and reunited to the fovea in three of eight rabbits with pin splints. In each case the fragment of the head of the femur united with

the neck, whereas healing occurred in only one of the five other animals in which the round ligament did not reunite. The neck of the femur in which the fracture healed without a ligamentous blood supply had been ligated so that nutrition to the tissues of the head attached to the neck was further disturbed. This marked disturbance of circulation had been compensated by collateral circulation to the tissues of the head from the shaft through the epiphyseal line. In this group of experiments no other collateral circulation developed to the head from the diaphysis through the epiphyseal plate.

The tissues of the united fragment were replaced by creeping substitution of new vascular connective tissue from the fovea (the ligamentum teres had reunited)



Fig. 9.—Revascularization and creeping substitution of the tissues of the head from the fovea centralis thirty-three days after intracapsular fracture and splinting of the head with a metal pin when the animal was 10 days old. There is good union of the fractured segment with little distortion of the epiphyseal line;  $\times 16$ .

and from the periphery of the neck (the blood supply from the capsule). Ultimately new bone replaced the necrotic tissue. In these cases the head was smaller than that of the controls, but from eleven to forty-four days after operation it was the same size or slightly larger than at the time of operation. Moderate flattening and anterior rotation of the head were noted, but there was no dislocation or abnormality of the acetabulum. The haversian gland tissue was hyperemic. When the fragments of the head did not unite after fixation, it became necrotic and ultimately liquefied within the joint space. The fracture surfaces of the neck

were covered by a layer of cartilage in which new secondary ossifying centers occasionally developed from the tissues of the head which remained attached to the epiphyseal line at the time of fracture. In most cases the cartilage plate was narrower because of the diminished blood supply, and the neck of the femur was usually short. The hypoplasia of the neck seemed great because of the downward displacement on the shaft, since growth had continued as usual in the metaphysis beneath the great trochanter.



Fig. 10.—The head of the right femur ( $\times 16$ ) shown in figure 8 C. Growth within the metaphysis has been restored, and the head is united completely despite poor alinement.

The head was completely freed from the right femur in five rabbits from  $1\frac{1}{2}$  to 5 days old, but it was too small for fixation. The fragments within the joint spaces were found later to be attached by fibrous tissue to the synovia or to the scar tissue about the joint capsule; one, however, had been displaced or liquefied. So far as could be determined, there was no growth of the ossification center in these fragments even forty-one days after operation. Usually new secondary ossification centers developed in the cartilage tissues of the head attached to the neck, but these were distorted and associated with considerable deformity and hypoplasia of the neck. The growth of the shaft from the metaphysis beneath the

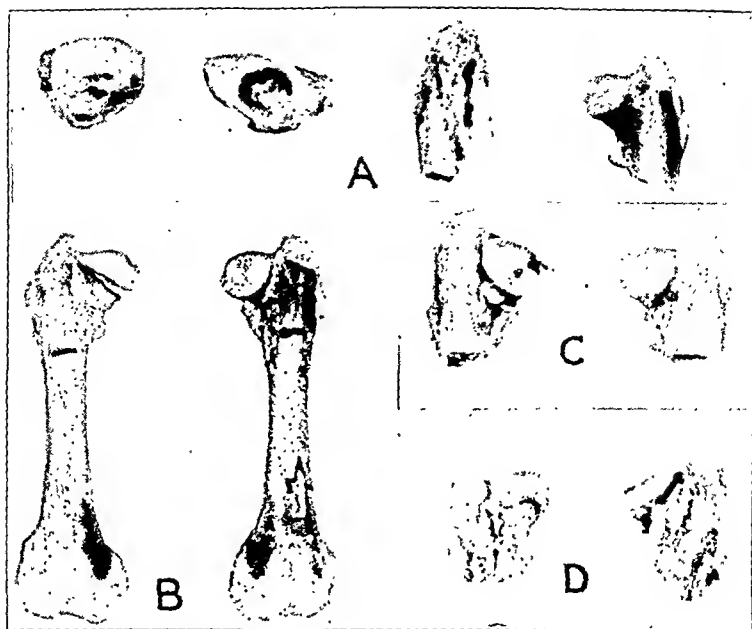


Fig. 11.—Femurs of rabbits after division of the right ligamentum teres and intracapsular fracture of the head. *A*, hypoplasia of the right acetabulum and neck forty-one days after operation, performed when the animal was 36 hours old. The fragment of the head liquefied within the joint space. *B*, necrosis of the head of the right femur and nonunion of the splinted fragment seven days after operation, performed when the animal was 32 days old. Repair of these fractures occurred rarely, except when the ligamentum teres reunited with the fovea centralis. *C* and *D*, ligation of the neck in addition to the aforementioned procedures. Periosteal collateral circulation is abundant, and union of the small depressed fragment of the head is firm (see also figure 12).

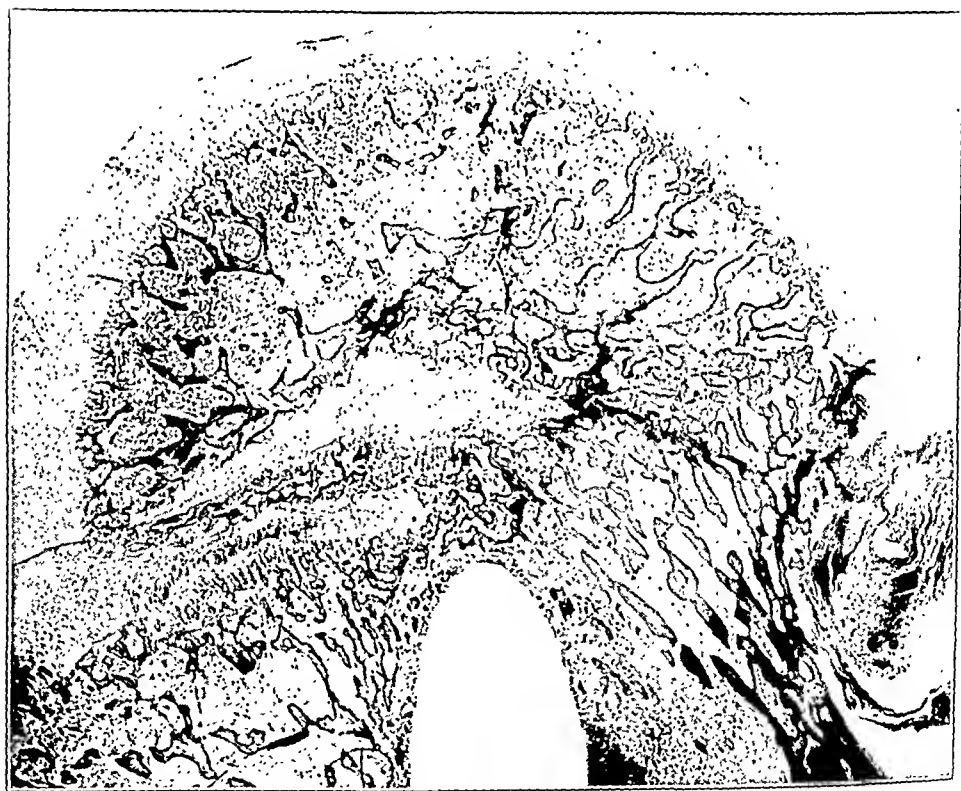


Fig. 12.—The head of the right femur ( $\times 16$ ) shown in figure 11 *C* and *D*. The necrotic tissues of the head are being revascularized and replaced by creeping substitution from the periosteum of the neck and medullary tissues of the shaft. Collateral circulation from the diaphysis to the head developed rarely and only after extensive interference with the blood supply to the head.

great trochanter was undisturbed. In one rabbit the ligamentum teres had become attached to new cartilage formed over the fracture surface of the neck.

There was also a marked tendency for the ligamentum teres to reunite in a group of rabbits in which a deep wound was made in the head of the femur without complete fracture. The necrosis produced was more marked, and healing was slower in these than in the control animals in which the ligamentum teres remained intact.

#### COMMENT

These studies of the effects of interference with the circulation of the femur in young rabbits emphasize the importance of several sources of blood for normal growth of the head and for the repair of injuries. Interference with circulation to the tissues of the shaft does not affect the head of the femur. The intervening septal plate of cartilage often is wider than usual, and the length of the neck of the femur is shorter because growth within the metaphysis has been disturbed. This indicates that the blood supply for cartilage proliferation in an epiphyseal plate is obtained from the corresponding epiphysis and that production of bone in the adjacent growth center depends on the circulation from the shaft. There are no appreciable vascular connections between the marrow tissue on the two sides of the plate. Osteogenic buds extend into the cartilage of the head in new-born and very young rabbits, but their connections with the metaphysis disappear soon after the formation of a secondary ossification center and an epiphyseal plate. In one rabbit collateral circulation developed through the plate to the tissues of the head after interference with the blood supply from the periosteum and the ligamentum teres. As noted previously, the epiphyseal cartilage after disturbance to the growth centers tends to disappear earlier than in the control bones. When the segment of the head of a fractured femur contains tissue from the neck and the ligamentum teres is uninjured, the osteoid structures of the neck attached to the segment become necrotic; so, also, but less marked, is the case of the tissues of the head remaining attached to the neck. Such changes indicate that the epiphyseal plate is not traversed by blood vessels.

The changes in the head of the femur of young growing rabbits following interruption of the ligamentum teres suggest that this ligament normally supplies part of the circulation to the head, particularly the tissues about the fovea centralis. This injury produces only a slight deformity of the head. When the periosteal blood supply to the head is destroyed, nutritional changes occur, especially in the peripheral tissues of this epiphysis. The disturbance in nutrition produced by the interruption of either of these sources of blood is temporary, for the other compensates and is adequate for the development of the head. This is demonstrated by hypertrophy and hyperemia of the ligamentum teres when the only source of blood is through this structure and by the growth of vascular granulation tissues about the lip of the head when the ligamentum teres has been cut. When both the periosteal and

the ligamentous blood supply have been interrupted, the tissues of the ligamentum teres attempt to reestablish continuity.

A fractured head separated from its attachments, in both adult and growing animals, may be revascularized and repaired by creeping substitution. This demands close approximation, good fixation of the fractured surfaces and, in growing animals, an adequate periosteal blood supply or reunion of the ligamentum teres. In adult animals the situation is slightly different, for there is no epiphyseal cartilage to act as a barrier to circulation between the medullary tissues of the shaft and of the head of the femur. Union of a fracture is impeded also when the periosteal blood supply is disturbed, although the ligamentum teres tissues are intact.

When the head is fractured in rabbits too small to permit fixation, the fragment grows and within a few days usually is larger than the control head. This increase in size seems due to the production of more articular cartilage, for the ossification center is no larger and frequently is slightly smaller than the center in the control. Absence of weight bearing on the head and the ability of articular cartilage to obtain nutrition from synovial fluid may explain this increase in the amount of cartilage. In rabbits only a few days old the blood supply from the periosteum seems relatively more important to the head of the femur than that through the ligamentum teres. The presence of more vessels of macroscopic size entering the periphery of the cartilage in the head than in the attachment of the ligament in young rabbits supports this view. The vascular connections with the fovea are established more slowly. The osteogenic buds for secondary ossification centers perhaps have a transient blood supply from the shaft through the epiphyseal cartilage.

These experiments are not concerned with the presence or absence of epiphyseal end-capillaries. They do, however, demonstrate that the larger medullary vessels from various external sources anastomose in the deeper tissues, so that if end-capillaries are present beneath the articular cartilage they do not depend necessarily on a particular source of blood.

The deformities of the femur produced in these experiments were caused by injury to the bone tissues and subsequent molding according to the stress of weight bearing and muscle tension. Possibly the loss of support by the ligamentum teres added to the distortion, although dislocation was rare and, when present, was attributed to the trauma of manipulation and injury to the joint capsule. The head was sometimes flattened over the neck, much as in the epiphysitis of the head of the femur which Legg, Perthes and Calvé described. The tendency to anterior rotation results from an adjustment to the lines of force in weight bearing, from a predominance of the internal over the external rotator muscles or from both. Internal rotation of the femur and consequent outward protrusion of the lower portion of the leg and foot

without noteworthy deformity of the head were noted in two control rabbits in which the short rotator muscle tendons were cut.

When the proliferation of epiphyseal cartilage for growth in the metaphysis of the neck was lessened, the neck was often short and at a decreased angle to the shaft (*coxa vara*). This hypoplasia of the neck was marked, especially in very young animals, so that often the length of the shaft from the base of the neck was considerably shorter than that in the control femur. The great trochanteric portion of the proximal epiphyseal plate was in the usual plane, transverse to the axis of the shaft, whereas the neck portion of the plate was more nearly parallel to the shaft and was elongated, as growth had proceeded in the usual way in the metaphysis beneath the great trochanter.

The large size of the head that had been fractured from the neck but not splinted was due to the increased growth of articular cartilage about the normal ossification centers. This acceleration of growth occurred because the separated fragment of the head carried no weight and was not confined within the acetabulum. It did not occur when the head was fixed to the neck after being fractured. When the fractured head of the femur, not splinted, continued to grow, it was not confined within the acetabulum, even though it was attached by the ligamentum teres, and the acetabular structure did not increase in size. Apparently the ligamentum teres alone was not sufficient to hold the head within the space during growth. This and the rarity of dislocation of the head of the femur following interruption of the round ligament indicate that this band of fibrous tissue is of little importance as a ligament.

The ability of joint tissues to reform articulating surfaces and to restore function completely is remarkable even in the case of marked injury and distortion of the bony parts, such as removal of the head of the femur. The reconstruction of the joint in these experiments was by growth of cartilage over the osteoid surfaces of the neck bared by the fracture and by the articulation of this new cartilage surface with similar new or old cartilage in or about the acetabulum. When necessary to support weight and to hold together articulating surfaces, fibrous tissue proliferated within the capsule. Small secondary centers of ossification often developed in the portion of head remaining on the neck when sufficient collateral circulation had been established. In one rabbit a few days old, after complete isolation of the head of the femur, the ligamentum teres became attached to the articular surface over such a new ossification center.

Results obtained in these experiments apply to young growing animals but not to adults. In the latter the bones are fully formed, they contain a relatively greater amount of osseous supporting tissue and there is medullary continuity of the epiphyses and the diaphysis. All the results cannot be transferred even to older growing rabbits, since the



epiphyses have attained more nearly full development. Some of the principles, however, such as regard necrosis and repair in an isolated fragment, and the general plan for collateral circulation should apply to all groups. The blood supply through the ligamentum teres in adult rabbits may not be sufficient to prevent complete necrosis of a fractured segment, but certainly it is important as a potential source when collateral circulation is needed. Other things being equal, an intracapsular fracture of an adult femur should heal more readily than that of a growing bone, since the medullary circulation is continuous throughout the bone after cessation of growth in length.

Traumatic injury to the tissues may have added to the circulatory disturbances produced in the femurs of these rabbits, but opening the hip joint and manipulating the bones alone produced no appreciable changes.

#### SUMMARY

The most important source of blood to the head of the femur in growing rabbits is through the small vessels entering this epiphysis from the periosteum where the capsule of the hip joint is attached at the margin of the articular cartilage. The ligamentum teres also contributes blood to the head, particularly to the tissues about the fovea centralis. If the blood supply to the capsule or to the ligamentum teres is interrupted, the remaining source will compensate for the loss and be adequate for repair of injury, for growth and for function of the part. Interference with nutrition of the metaphysis of the neck of the femur does not affect the tissues of the head, except by widening the intervening septal plate as a result of diminished ossification of cartilage.

There is no noteworthy vascular connection between the medullary tissues of the shaft and the head through the intervening cartilage plate. Collateral circulation rarely develops through the plate, and then only after marked vascular disturbance to the head of the femur. Proliferation of cartilage in an epiphyseal plate depends on the circulation of the epiphysis, and the blood to the metaphyseal growth regions is supplied by the shaft. Separation of the head of the femur occurs through the cartilage line in the plane between the limits of the epiphyseal and the metaphyseal circulation.

The repair of an intracapsular fracture through the head of the femur in growing rabbits is retarded if either of the two principal sources of blood to the head is interrupted. Interference with the ligamentum teres and complete intracapsular fracture of the head produce marked necrosis of the loose fragment, which may be revascularized and replaced by new bone if it is fixed in apposition with the fracture surface of the neck. This creeping substitution proceeds from the vascular granulation tissue at the periphery of the neck where the joint capsule is attached.

Vascular disturbance to the head of the femur accentuates the remaining possible sources of blood. The severed ligamentum teres tends to reunite with the fovea when the capsular supply also is interrupted. In the experiments one ligament became attached to the new cartilage formed over the fracture surface of the neck. Beneath this new articular cartilage was a small new secondary ossifying center.

Not only will the head of the femur in young rabbits continue to grow when attached only by the ligamentum teres, but in a few days it may become larger than the control head. This increase in size is due to the increase in the amount of cartilage, probably because the part has no weight-bearing function. The development of the acetabulum depends on the integrity and growth of the head of the articulating femur.

Deformities of the head and neck of the femur in young rabbits resulting from nutritional disturbances of the head vary according to the extent of the injury, the mechanical stress of weight bearing (flattening of the head and coxa vara), the muscle pull (anterior rotation) and the inhibition of growth in the metaphysis of the neck. Other things being equal, the degree of deformity is inversely proportional to the amount of osseous supporting tissue present, which depends on the age of the animal. The blood supply to the head must be adequate for the proliferation of cartilage in the epiphyseal plate in order to obtain normal growth and development of the proximal end of the femur. Hypoplasia in the metaphysis of the neck results in a diminution in the growth of that portion of the femur between the lower epiphysis and the base of the neck, while the total length of the bone is the same as that of the control, owing to growth, as usual, in the metaphysis of the great trochanter.

Disturbances of the external sources of blood and trauma to the head of the femur in adult rabbits probably do not cause all the changes noted in growing rabbits. Obliteration of the proximal epiphyseal cartilage plate when growth in length ceases establishes diaphyseal circulation to the head and makes other sources of blood less significant. This probably accounts for the dearth of blood vessels in the round ligament in adults. The potential sources of blood to a fragment of a fractured head of an adult femur, however, are the same as those in growing bone; if the ligamentum teres provides sufficient blood for viability of the fragment, it should unite more readily than in the growing femur, because of the supply of diaphyseal blood to the fracture of the neck.

The extent to which these observations on rabbits may be transferred to man is questionable, but certainly the underlying principles are important for understanding of disease and trauma of the head of the femur.

# TRAUMATIC ARTERIOVENOUS FISTULA INVOLVING THE RIGHT FEMORAL ARTERY AND VEIN

## SPONTANEOUS CLOSURE

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An arteriovenous fistula seldom becomes closed without surgical intervention. In the following case spontaneous closure occurred.

### REPORT OF A CASE

A man 44 years of age recently was seen at the clinic. He had an arteriovenous aneurysm of the right femoral artery and vein, but this condition was not his reason for seeking medical aid. In fact, the arteriovenous fistula had closed spontaneously about seven years before. The end-result was identical with that which would have followed ligation of the artery and the vein.

The patient had first registered at the clinic in 1924, because of the presence of a swelling in the right thigh, which emitted a bruit and gave the sensation of a purring cat to the palpating hand. For some reason he did not wait for an appointment but left Rochester before physical examination or any laboratory studies had been carried out.

The patient was brought to the clinic by his relatives in August 1935, because of dementia paralytica.

At the age of 11 years the patient received a bullet wound in the right thigh. An arteriovenous fistula (fig. 1) developed at the site of the wound. The usual train of events under these circumstances ensued, namely, the development of varicosities and associated swelling of the limb. He had worn an elastic bandage for twenty years. He had been aware of an inequality in the length of the legs and had had the heel of the left shoe built up, so as to facilitate walking. A bruit and thrill had been present until seven years before his last registration at the clinic.

Physical examination revealed conditions associated with syphilitic infection of the central nervous system, which require no further comment. There was a swelling in the right thigh, measuring 6 by 8 cm., which represented the thrombosed aneurysmal sac. At this time the signs of arteriovenous communication could no longer be elicited. The right tibia was 4 cm. longer than the left (fig. 2); the femurs were of equal length (fig. 3). There was an unusually strong pulsation in the right femoral artery, but the right popliteal, right dorsalis pedis and right posterior tibial arteries could not be palpated. Despite this condition the circulation in the right limb was adequate; blanching was minimal when the leg was elevated, and the blood returned promptly when the limb was lowered. There was no history of claudication.

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From the Division of Medicine, the Mayo Clinic.

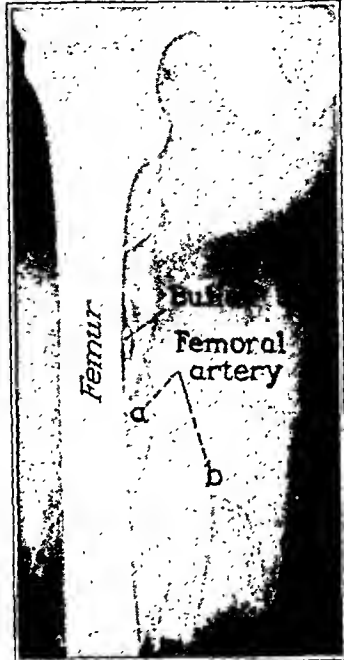


Fig. 1.—Arteriogram showing the femoral artery, with interruption between points *a* and *b*.



Figure 2

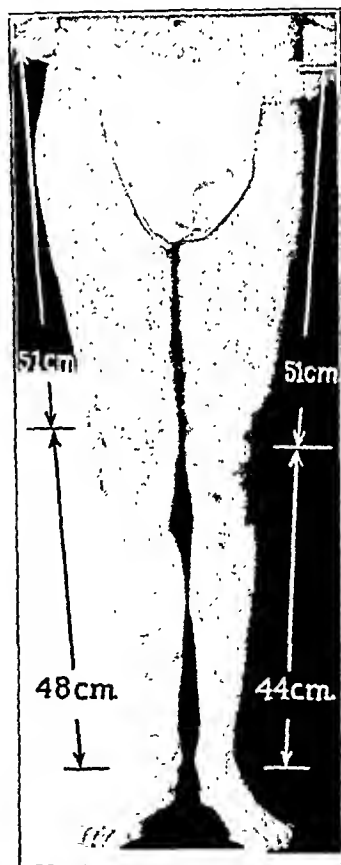


Figure 3

Fig. 2.—The right leg is thicker and longer than the normal left leg.  
 Fig. 3.—The right leg is longer than the left; the thighs are the same length.

An arteriogram of the right femoral artery was made by injecting into it 40 cc. of colloidal thorium dioxide. As previously described,<sup>1</sup> the artery was closed by digital pressure just proximal to the site of injection, and closure was maintained while a series of roentgenograms was made as quickly as possible. In the course of this procedure an unusually strong pulsation was noted in the femoral artery. Figure 1 illustrates the interruption of the femoral artery at the site of the thrombosed aneurysmal sac. Cardiac hypertrophy was not present, and physical examination did not reveal any other abnormality.

The oxygen content of the blood which was obtained from the right femoral vein was 12.7 volumes per cent, and the oxygen capacity was 19.5 volumes per cent. The oxygen saturation, which is obtained by dividing the oxygen content by the oxygen capacity, was 65.1 per cent, indicating that there was no mixing of venous with arterial blood and that closure of the fistulous communication was complete.

#### COMMENT

While it is possible for a recently acquired arteriovenous fistula to heal spontaneously,<sup>2</sup> we were unable to find any reference in the literature to an occurrence similar to the one that we are reporting. In fact, a survey of the pathologic physiology of such a fistulous communication affords the explanation for the extreme rarity of such a possibility and the explanation for the usual course of progression unless surgical intervention is resorted to. Since the pressure in the venous channels is considerably lower than that in the capillary bed, the blood follows the path of least resistance and causes a progressive dilatation of the involved vein and its tributaries. This condition produces changes in the venous walls, which have been described as "arterialization," as well as subsequent changes commonly encountered under these circumstances. If the arteriovenous communication is large, a considerable amount of blood will be shunted away from the general circulation, and presently there will occur a corresponding dilatation of the artery and vein proximal to the fistula. In the present case the artery proximal to the fistula was unusually large, and there can be little doubt that the fistulous communication must have been rather large before its closure. Ordinarily, as Holman<sup>3</sup> showed, "this dilatation is progressive and will continue until the resistance offered by the fistula plus the resistance to any further dilatation of the vessel leading to it equal the resistance which exists in the capillary bed elsewhere." The result of diverting a goodly proportion of arterial blood from the natural channels is similar in its

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1. Horton, B. T.: Arteriovenous Fistula Involving the Common Femoral Artery Identified by Arteriography, *Am. J. M. Sc.* **187**:649 (May) 1934.

2. Pemberton, J. deJ.: Arteriovenous Aneurysm, *Arch. Surg.* **16**:469 (Feb.) 1928.

3. Holman, Emile: Arteriovenous Aneurysm: Clinical Evidence Correlating Size of Fistula with Changes in the Heart and Proximal Vessels, *Ann. Surg.* **80**:801 (Dec.) 1924.

effect on the heart to an aortic regurgitation with resulting cardiac enlargement. We have, unfortunately, no information regarding the previous cardiac status of this patient, but during the seven years following the natural and yet unexplained closure of the arteriovenous fistula there could have been the same decrease in the size of the heart as has frequently been shown to occur after surgical obliteration of the abnormal communication.

The long duration of the fistula in itself is no explanation for the closure. In many of the cases reported in the literature,<sup>4</sup> arteriovenous fistulas in the same anatomic situation have been present for twenty-five years or more without coming to the same fortuitous termination. In other situations they have existed as long as fifty-five years, as in a case of aneurysm of the vessels of the wrist which was reported by Scottin;<sup>5</sup> therefore, the long duration in itself does not explain the natural cure.

The question may be raised as to the part the syphilitic infection played in the closure of the fistula. Regarding this, nothing can be stated with certainty, but the probability is that there was no relation.

Interestingly, many attempts have been made to close arteriovenous fistulas by nonsurgical means, such as injection of coagulating fluids, for instance, solution of ferric chloride, and the use of galvanopuncture.<sup>4</sup> Most of these efforts have resulted in failure, in secondary hemorrhage with gangrene, in loss of the limb or, in some instances, even in loss of life. Guattini,<sup>6</sup> in 1785, succeeded in curing a brachial aneurysm by a combination of direct pressure in the region of the fistulous communication and indirect pressure—or digital obliteration of the afferent artery. Vanzetti, Monteggio and Brambilla<sup>7</sup> are credited with similar cures, but these results were the exception rather than the rule, and even these conservative procedures were known to cause inflammatory changes about the sac and at times to result disastrously.

This case presents several other interesting features. First, despite the fact that the fistulous communication was in the upper part of the thigh, the increase in growth of bone was in the tibia rather than in the femur. An adequate explanation of this phenomenon cannot be given. Second, the actual occurrence of increase in length of the bone, although usually seen in the congenital form of arteriovenous fistula,<sup>8</sup> has rarely

4. Callander, C. L.: Study of Arteriovenous Fistula with an Analysis of Four Hundred and Forty-Seven Cases, *Johns Hopkins Hosp. Rep.* **19**:259, 1920.

5. Scottin, quoted by Callander.<sup>4</sup>

6. Guattini, quoted by Callander.<sup>4</sup>

7. Vanzetti, Monteggio and Brambilla, quoted by Callander.<sup>4</sup>

8. Horton, B. T.: Hemihypertrophy of Extremities Associated with Congenital Arteriovenous Fistula, *J. A. M. A.* **98**:373 (Jan. 30) 1932.

been reported in association with the acquired type. The fact that the fistula was established in early life is the explanation of this phenomenon.

#### SUMMARY

Our object in reporting a case of acquired arteriovenous fistula of the femoral artery and vein is to describe a unique circumstance: A condition which inherently has a natural trend of progression came to a spontaneous cure after being present for approximately twenty-five years, an event which, as far as we are able to ascertain, has never previously been recorded.

# SURGICAL TREATMENT OF IDIOPATHIC HYPERTROPHY OF THE BREAST

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The majority of women with noninflammatory, nondegenerative and non-neoplastic hypertrophy of the breast complain of no symptoms apart from slight inconvenience occasioned by the enlarged glands and require no treatment. Frequently, however, the hypertrophy assumes such proportions as to cause physical, occupational or psychic embarrassment, and so becomes a condition demanding relief.

Logical treatment for this type of hypertrophy would be directed to removal of the stimulus toward abnormal growth, but since it is yet unknown, such treatment is unavailable. It is hoped that added interest and more careful study may reveal the underlying defect and thus lead to more rational therapeutics. Attempts to correct the condition by organotherapy, iodides, roentgen therapy, bandaging and a host of other measures have brought negligible results. When other treatment has failed and the symptoms justify the hazard of operation, plastic surgery offers a well defined technic for alleviating the hypertrophy.

Since Lexer's article published in 1923, plastic surgery of the breast has made tremendous progress. Although the end of the possibilities has not been reached, the present status of the procedure is sufficiently standardized to warrant operation with reasonable assurance that the surgeon will reduce the size of the breast, give it a normal configuration and location, transfer the nipple and areola to their proper place on the reduced breast and at the same time preserve the blood supply and disturb the function slightly, if at all.

In each particular instance the surgeon must critically study the indication to determine whether operative intervention is justified; he must be especially cautious in view of the fact that spontaneous regression is possible. The desirability of the reconstruction cannot be left entirely to the whim of the patient, despite the minor character of the operative procedure.

## PRELIMINARY OBSERVATIONS

*Anatomy of the Normal Breast.*—Before describing the operative procedure, it is essential to refer briefly to the more salient anatomic features of the normal breast, since the aim of the technic is to reconstruct the hypertrophied breast and yet to preserve its blood supply and secretory function.



The breast is a hemispheric, racemose gland, protruding from the chest as a conical disk, enclosed in two layers of superficial fascia. The anterior layer sends trabeculae into the skin (ligaments of Cooper), which account for the firmness of the breast and the difficulty encountered in separating the skin from the gland. The posterior layer sends trabeculae into the deep fascia covering the pectoralis major muscle. This attachment is loose and permits free shifting of the breast on the chest wall. Between the posterior layer of the superficial fascia and the deep fascia covering the muscles of the chest is loose cellular space; it facilitates the separation of the gland from the underlying muscle.

Aside from the prolongations given off anteriorly to the skin and posteriorly to the pectoral fascia, the superficial fascia sends trabeculae

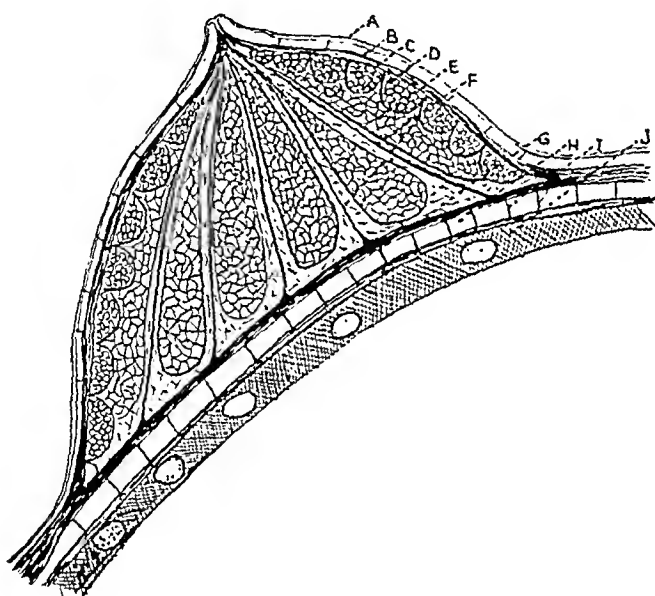


Fig. 1.—Sagittal section of breast. *A* indicates the skin; *B*, the ligament of Cooper; *C*, the superficial layer of superficial fascia; *D*, fatty tissue; *E*, glandular tissue; *F*, trabeculae; *G*, the deep layer of superficial fascia; *H*, cellular space; *I*, trabeculae; *J*, pectoralis major.

into the breast substance, which divide it into from twelve to fifteen wedge-shaped lobes, radiating from the nipple. Each lobe has a main duct opening on its summit. These lobes may be considered miniature mammary glands, each functionally and anatomically independent; thus a lobe can be removed without material interference with the function of the rest of the organ.

The entire breast is covered with a layer of fat of variable thickness; it invades the interlobular structures and disappears in and around the areola. It is this fatty tissue rather than the glandular tissue that determines the size of the breast (fig. 1).

The dimensions of the normal gland are variable, depending on age, race, climate and physiologic state. The average virginal mammary gland is from 10 to 15 cm. in diameter and weighs from 140 to 200 Gm. It projects from the chest wall 5.5 cm., at an angle of 30 degrees. At its summit it shows the areola to be 4 cm. in diameter, in the center of which is the nipple, 1 cm. in diameter, at an elevation from the areola of from 1 to 2 cm. The nipple is located over the fourth or fifth interspace, 12 cm. from the midline. It is composed of nonstriated, circular and longitudinal muscle, blood vessels and lactiferous ducts.

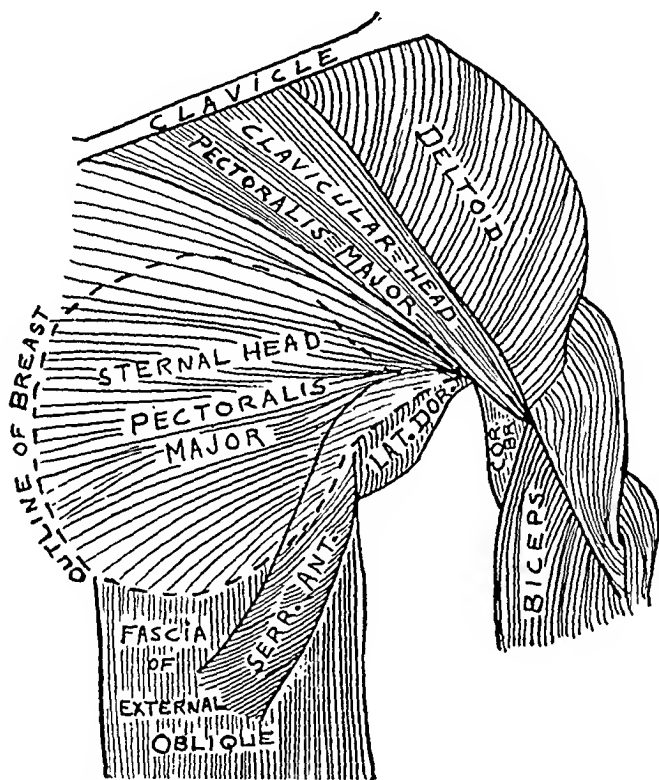


Fig. 2.—Extent of the breast on the chest wall.

The base of the breast is roughly hemispherical and extends into the axilla. The upper curve lies on the pectoralis major and serratus anticus muscles, two thirds of the gland resting on the former; the lower curve is situated on the obliquus internus and rectus abdominis muscles (fig. 2). The axillary tail lies on the serratus anticus and pectoralis major muscles and extends to the third rib in the axilla, gaining entrance into this space by an opening in the axillary fascia. This prolongation is the only part of the gland beneath the deep fascia; therefore, its emeculation is more difficult than that of the rest of the gland.

The extent of the breast is variable and is underestimated in the usual anatomic description. It extends from the second to the sixth

or seventh interspace vertically and from the middle of the sternum to the middle of the axilla horizontally. Each breast may be divided surgically into four quadrants by two oblique lines; the first starts from the sternum at the level of the third costal cartilage and runs downward and outward to the seventh rib in the midaxillary line; the second begins at the third rib at the anterior axillary fold and extends downward and inward to the sixth costal cartilage, at a point between the angle of the cartilage and the attachment to the sternum.

*Blood Supply* (fig. 3).—The principal arterial supply to the breast is obtained from the following vessels:

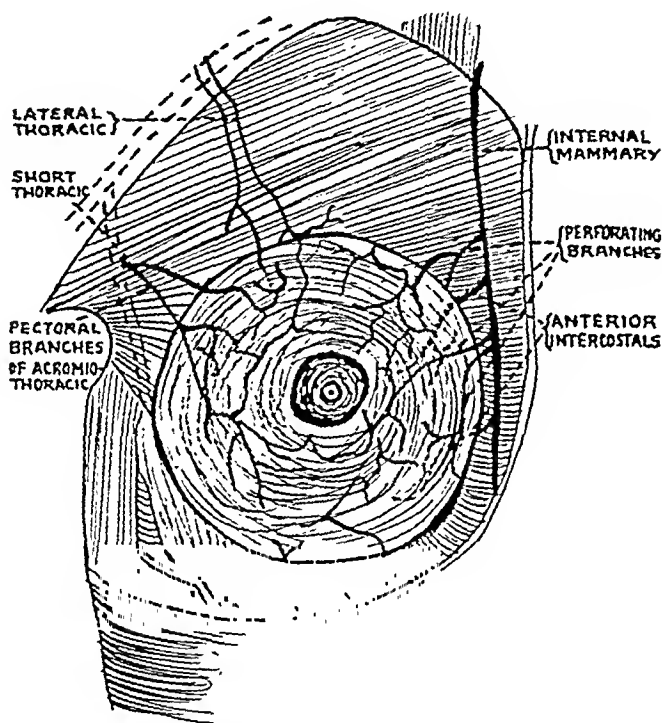


Fig. 3.—Blood supply of the breast.

1. The internal mammary artery, which gives off perforating branches, especially the second, third and fourth, and the anterior intercostal arteries. The former emerge from the intercostal space on each side of the sternum, pierce the pectoralis major muscle, turn outward and give off superficial branches, which supply the skin, superficial fascia and anterior surface of the breast. The deep branches supply the parenchyma and break up into a network around the areola. The anterior intercostal arteries lie between the deep layer of the superficial fascia and the deep fascia, enter the posterior surface of the gland and anastomose with the aortic intercostal arteries. These vessels form two plexuses: (a) a subareolar plexus, formed by superficial branches that

give off branches to the nipple, areola and adjacent parenchyma; (b) a deep plexus, composed of deep branches which emerge from the base of the organ and send branches to the parenchyma and stroma.

2. The lateral thoracic (long thoracic or deep external mammary) artery, which arises from the second part of the axillary artery, descends along the lateral border of the pectoralis minor muscle and anastomoses with the intercostal and subscapular arteries and with the pectoral branches of the thoraco-acromial artery, which supplies the upper lateral quadrant.

3. The short thoracic (superficial external mammary) artery, which is a branch of the third division of the axillary artery, or the first portion of the brachial artery, passes through the superficial fascia of the axilla, anastomosing with the long thoracic artery.

4. Pectoral branches from the acromiothoracic artery anastomose with the foregoing vessels to supply the supralateral quadrant.

The superficial veins form a circle around the base of the nipple (circulus venosus of Halle). From this anastomosing circle large branches run to the periphery of the gland and empty into the external jugular, axillary and internal mammary veins. The deep veins accompany the arteries.

*Pathologic Process.*—There are several varieties of idiopathic hypertrophy:

1. Congenital

2. Acquired

(a) Puberty (virginal, glandular, parenchymatous)

(b) Adult

(1) Hypertrophic (adipose pendulous)

(a) Fatty degeneration

(b) Fatty infiltration

(2) Atrophic (flabby pendulous)

The congenital type is rare and is considered to be a manifestation of precocious sexual development. Malleat described a case in which hypertrophy existed at birth and menstruation began at fifteen days after birth.

In the type that begins at puberty the breast continues to enlarge beyond normal limits. Dunston reported a case in which one breast weighed 64 pounds (29 Kg.). In Deaver and McFarland's collection of one hundred and eighty-two cases, the hypertrophy was bilateral in one hundred and forty-two instances and limited to one breast in forty.

The histologic changes are indefinite. Specimens sent to the laboratory reveal hyperplasia of the pericanalicular and periacinar fibrous stroma, with new formation of acini and ducts or fatty hyperplasia, with

little glandular tissue. Lewis stated the belief that gynecomastia, virginal hypertrophy and fibro-adenoma represent different phases of the same pathologic process and may have the same etiologic factor.

The adult type begins with pregnancy or lactation. It may be associated with generalized adiposity or be present as localized fatty infiltration or degeneration.

The atrophic form represents senile involution; the skin hangs on the chest wall like an empty sac, containing little or no breast tissue. This condition may be abnormal in the amount of tissue present or in the time of its appearance (premature).

*Symptoms.*—The enlargement occurs slowly, requiring from one to ten years for its full development. Early in the process there is no change in contour, and the hypertrophied organ differs from the normal breast only in size. There are no symptoms at this stage except those arising from the inconvenience of the enlargement. Later, when the increasing weight makes traction on the fixation apparatus, the skin, suspensory ligament and retromammary fascia give way, and a pedicle is created from which the hypertrophied breast hangs.

The subsequent symptoms are mainly mechanical. Striae appear, due to stretched and torn connective tissue. The skin of the areola becomes flattened and bluish. As a result of the mechanical disturbance of the circulation, edema develops, and veins are seen coursing beneath the skin. Maceration dermatoses appear in the submammary folds.

The patient complains of aching pains and inability to engage in occupations and sports, in which freedom of movement is essential. This situation leads to social maladjustment and depression, and the patient feels excluded from those phases of life which women anticipate with pleasure. In time she may present not only a surgical but an economic problem.

On physical examination the breast as a whole feels solid. The prolongations of connective tissue from the skin to the gland become tense and separate the fat into isolated nodules; this nodularity is palpable on the anterior surface, if the layer of fat permits. The nipple is flattened, is flush with the surface and at no time shows retraction. The posterior surface of the gland is never adherent to the pectoralis muscle.

*Diagnosis.*—Diagnosis is obvious, though mistakes have been made. The size and configuration of the breast are characteristic, and the absence of symptoms other than those attributable to great weight gives rise to little doubt as to the nature of the malady. A neoplastic hypertrophy shows definite features, such as irregularity of the shape of the breast, retraction of the skin and nipple, hard nodularity, fixation and metastasis. An inflammatory condition gives characteristic clinical signs.

The only difficulty in diagnosis is in differentiating the condition from generalized cystic degeneration, which gives rise to signs and symptoms identical with those of idiopathic hypertrophy. The distinguishing features may be so fine as to defy diagnosis. It is obvious that systemic involvement or obstruction to the circulation, such as that in elephantiasis, must be ruled out.

#### TECHNIC

*Location of the New Areola.*—To determine the location of the new nipple, a line is drawn from the center of the clavicle to the anterior superior spine of the ilium and another from the xiphoid process to the anterior axillary web and another from the xiphoid process to the

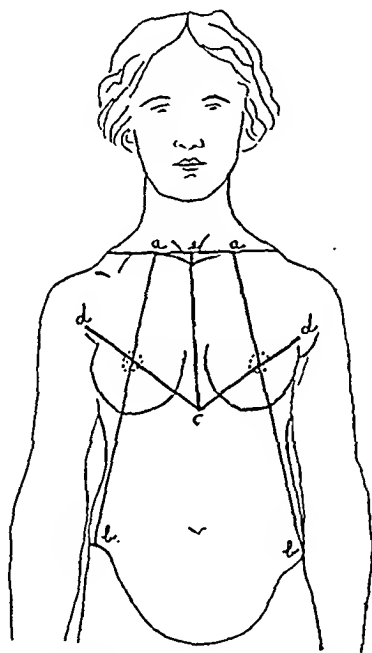


Fig. 4.—Location of the new areola (*a-b* indicates the line from the center of the clavicle to the anterior superior spine of the ilium; *c-d*, the line from the xiphoid to the anterior axillary web; *e-e*, the midsternal line).

anterior axillary web. The intersection of these lines is the approximate point for the location of the nipple. Similar lines are drawn on the opposite side, and a midsternal line is made for comparison between the two sides. The points thus determined are marked by a superficial scratch made with the point of a scalpel (fig. 4).

*Approach to the Breast.*—At the point thus indicated, a circle of skin and fascia, about 4 cm. in diameter, is excised to the fatty layer. From the inferior margin a vertical incision is carried just through the skin, as far as the dislocated areola. From this point the incision is continued around the circumference of the areola, enclosing an area equal in diameter to that of the aperture already prepared. A second

concentric incision is made outside the first at a distance of 2 cm. It is most important that these incisions should not extend deeper than the corium, in order to preserve the circulation.

The skin between the two circular incisions is carefully separated, in a manner similar to raising a full thickness skin graft. Beisenberger forcibly ablated the skin with a hemostat, baring a glistening, whitish corium (fig. 5A). The purpose of this careful dissection is to avoid damaging the superficial anterior areolar plexus of blood vessels and nerves. The areola remains attached to the breast only by fibers of

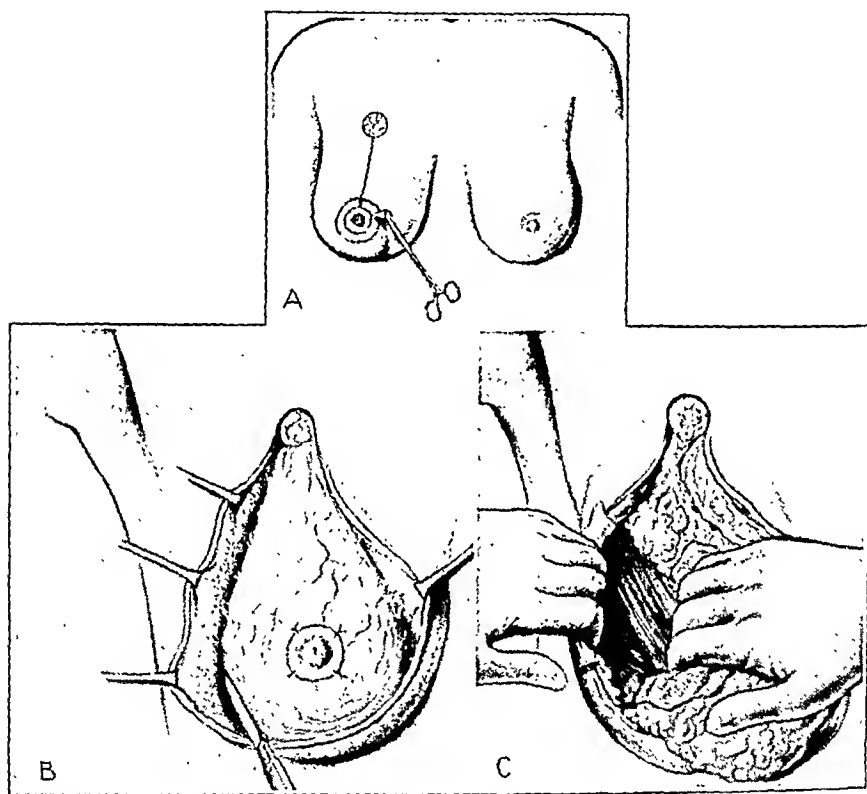


Fig. 5.—A, the aperture for the new areola; incision for exposure of the breast; circumareolar skin ablated with hemostat to preserve the areolar plexus. B, temporary sutures fixing the areola; skin dissection. C, enucleation of the breast.

connective tissue from the superficial fascia, blood vessels and lactiferous ducts. In order to prevent its being torn out or twisted inadvertently, the areola is fastened to the underlying tissues by four temporary silk sutures (fig. 5B).

The margin of the incision is everted with hooks, and the skin is separated from the superficial fascia by cutting the prolongations, which extend from the fascia to the skin (ligament of Cooper). Care must

be taken not to perforate the skin (fig. 5B). The dissection is continued until the skin adjacent to the incision has been separated for a distance of from 4 to 5 cm. The purpose of this superficial dissection is to preserve the venous circle at the summit of the breast. It is important that no further dissection be made on the medial side, which must serve as a pedicle for the breast in its new position and which carries the second, third and fourth perforating and intercostal branches of the internal mammary artery and the aortic posterior intercostal artery.

On the lateral side where the superficial fascia is attached to the skin, an incision is made through the fascia into the fatty layer covering the breast. The lateral tissues are retracted with the left hand; the right hand, protected by a pad of gauze, acts as a blunt dissector,

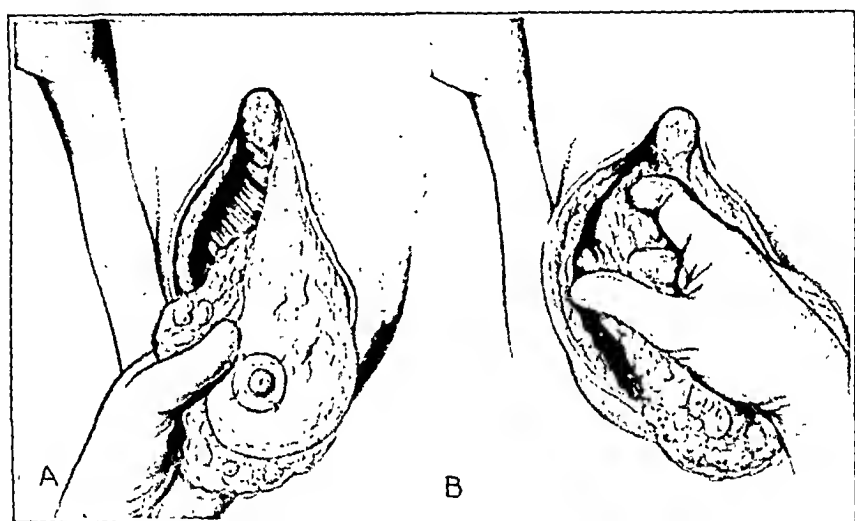


Fig. 6.—*A*, delivery of the breast, showing a wide medial pedicle. *B*, enucleation of the axillary prolongation.

separating the breast from the skin, to which a good layer of fat remains attached. The dissection is continued to the midaxillary fold and to the most dependent portions of the breast (fig. 5C).

So far there has been little bleeding, as the dissection has not been carried beyond the fatty layer and no important blood vessels have been encountered.

*Delivery of the Breast.*—By placing the hand in the retromammary space, the breast may be easily shelled out. The axillary border of the pectoralis major muscle is exposed, and it stands out prominently. A few restraining strands of connective tissue, passing from the breast to the deep fascia, may demand incision. Care should be taken to avoid cutting the medial perforating branches of the intercostal arteries (fig. 6A). Slight difficulty may be encountered in delivering the axillary



tail of the gland, since it lies beneath the deep fascia, which has to be cut. After division of the fascia, the finger is passed into the axillary space, and the axillary prolongation is enucleated (fig. 6B). The breast may be lifted entirely from its bed; it remains attached only at the sternal border by a pedicle from 4 to 5 inches (10 to 12.5 cm.) in width, which extends from the second to the seventh costal cartilage and carries nerve, blood and lymph supply. As long as this pedicle remains intact there is no danger of necrosis resulting from interference with the blood supply.

*Reduction.*—With the lateral portion of the delivered breast in the left hand, the amount of excess tissue is estimated, and with a clean excision the surplus in the infralateral quadrant is removed (fig. 7A). The supralateral quadrant is conserved to prevent damage to the lateral

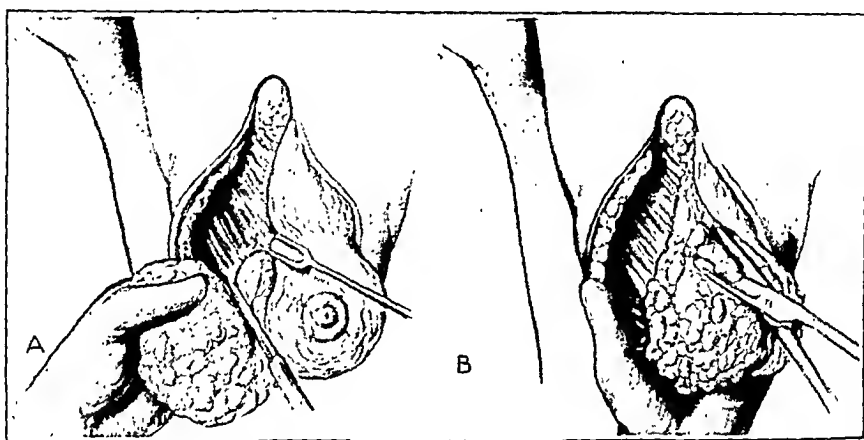


Fig. 7.—A, excision of surplus tissue in the infralateral quadrant. B, shaping of the lateral margins preparatory to rotation.

thoracic branches of the axillary artery. The remaining breast tissue is shaped ventrally and dorsally, so that it tapers toward the periphery; as much of the central breast substance as possible is left intact. (fig. 7B).

*Molding.*—A supralateral incision is made through the entire thickness of the denuded portion of the breast, so as to permit rotation of the lower segment under the upper (technic suggested by Clauue). The lower lateral pole is plicated under the supralateral quadrant, thereby elevating the breast on the thorax and causing it to assume a hemispherical shape (fig. 8).

*Fixation.*—The plicated flaps are sutured to each other, and the base of the gland is fixed to the pectoral fascia and muscle with catgut. The number of sutures required is a matter of personal preference; I use two or three for the gland flaps and from eight to ten for attaching the base to the pectoral muscles and fascia (fig. 9).

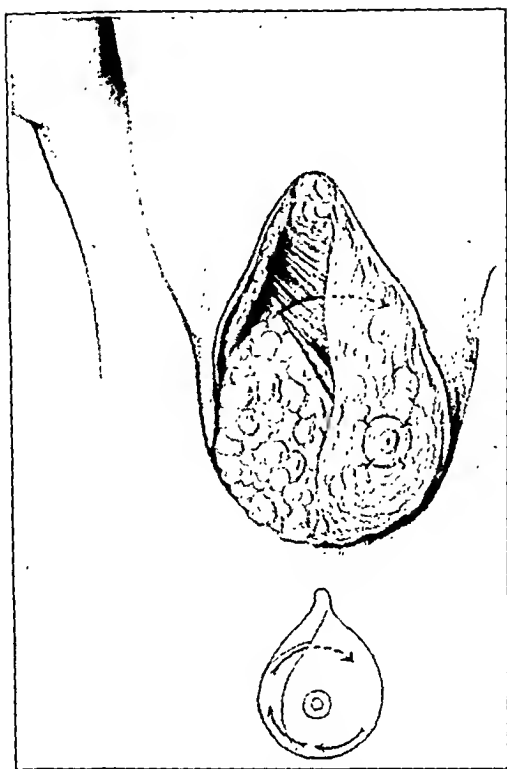


Fig. 8.—Rotation of the inferior pole under the supralateral quadrant.

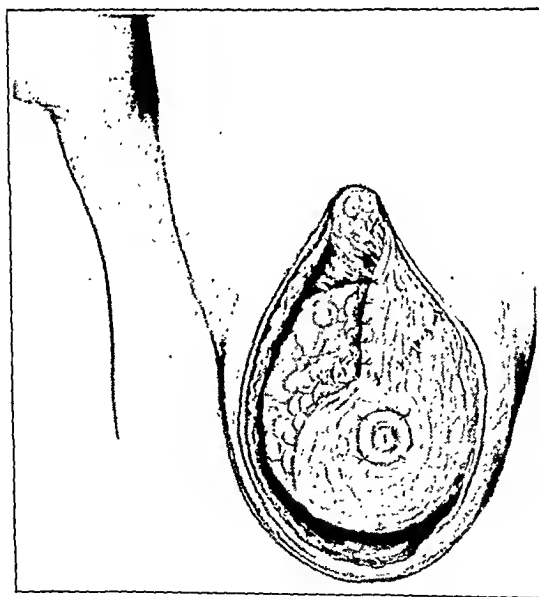


Fig. 9.—The breast rotated, flaps fixed to each other and to the chest wall.

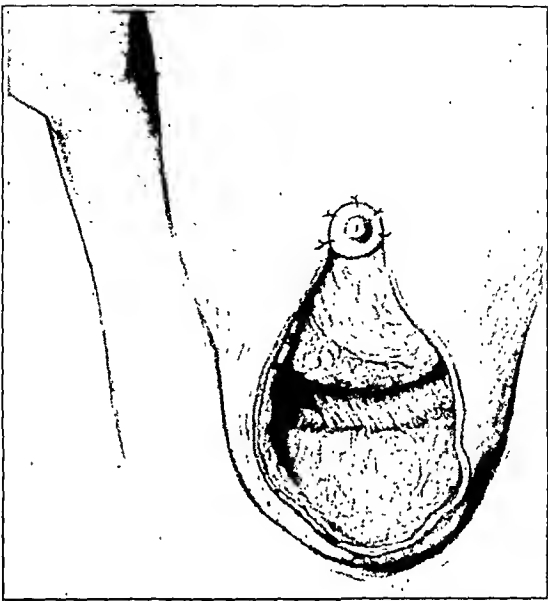


Fig. 10.—The transplanted areola sutured to the skin.

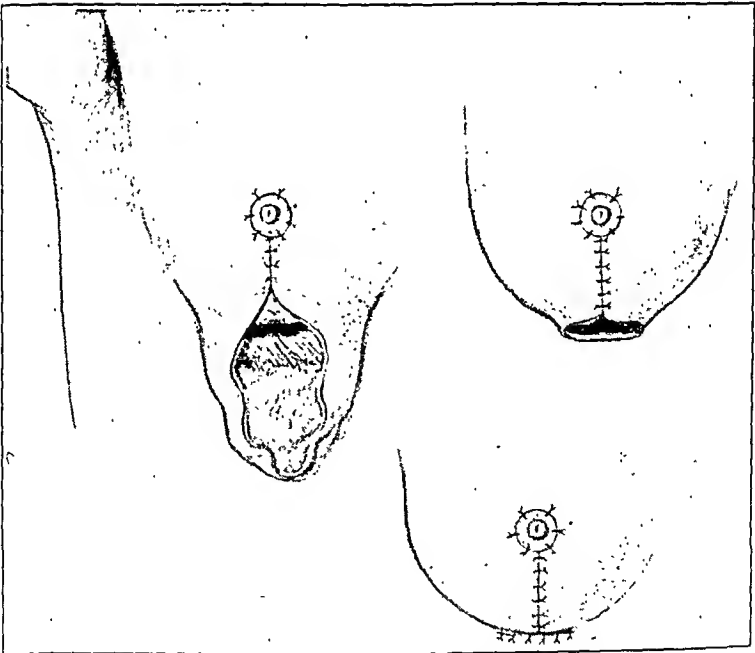


Fig. 11.—Management of redundant skin.

*Transplantation of the Areola.*—The edges of the areola are undermined for about 1 cm., to prevent constriction of the blood vessels should inadvertent torsion take place. It is placed in the new aperture previously made for it, and the initial four silk retaining sutures are

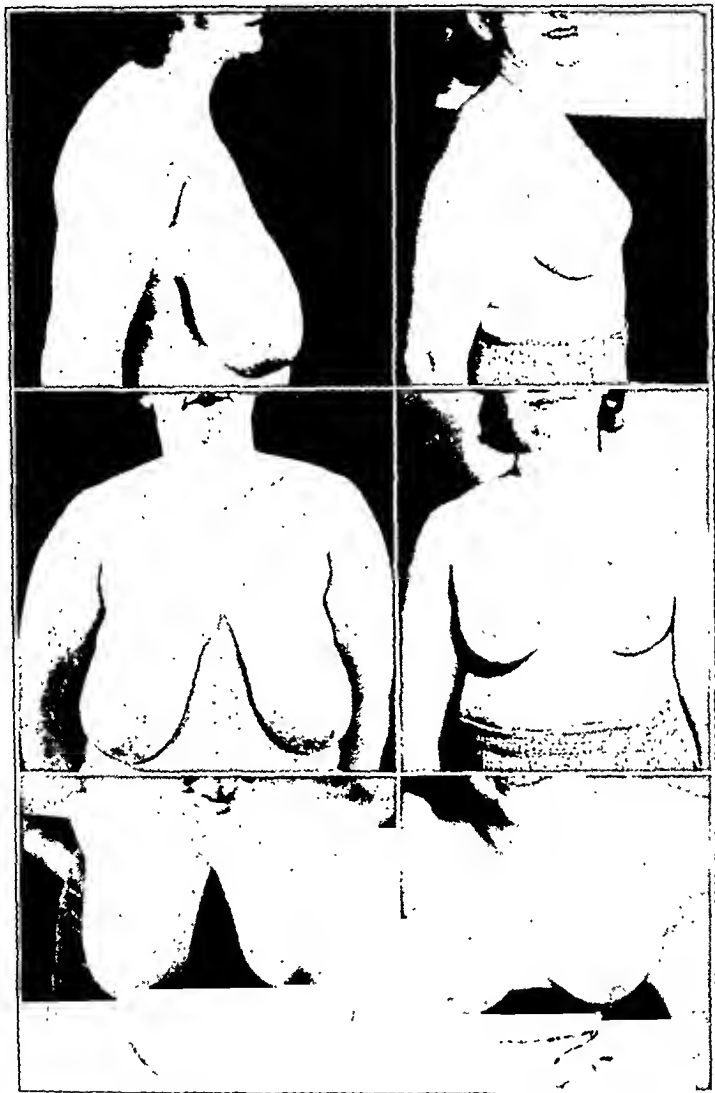


Fig. 12.—Views of a patient before and after operation.

removed. The areola is fixed in its new bed by four subcutaneous catgut sutures; care is taken not to rotate the nipple. The balance of the fixation is done by fastening the areola to the skin with horsehair, using about four sutures to the inch (fig. 10.)

*Removal of Redundant Skin.*—Redundant skin in the axillary region is fixed to the superficial fascia with as many catgut sutures as are necessary to obliterate dead spaces.

The skin is laid loosely over the reduced breast and held in place by ordinary towel clamps. At this time an idea of the amount of skin to be removed is obtained. As the skin offers no support, a minimum should be excised; even a slight redundancy is permitted. Because of its inherent elasticity it will spread itself evenly over the smaller breast. Excision of the skin below the areola is made from above downward. The edges are coapted with interrupted on-end mattress silk sutures, and the towel clamps are not removed until the sutures have been placed.

At the base of the gland a semilunar excision of skin is required before the line of suture can be continued. It may be possible to elongate the denuded area by a hook placed at either end so that the suture is continued in a vertical line. Frequently it is necessary to close the remaining wound transversely (fig. 11). Scarring is not considerable if a minimum of skin is removed.

*Dressing.*—Two rubber drains are placed at the dependent angles of the wound and removed in twenty-four hours. Occasionally it is advisable to pass a counterdrain into the axilla through a cutaneous incision made for that purpose. A copious dressing is applied with sufficient pressure to prevent collection of hematomas. Biddle suggested that pressure be obtained by the use of a bag inflated to a pressure of 20 mm. of mercury. I have had no experience with this dressing, but it seems to be a good procedure.

*After-Treatment.*—Although the operation borders on being a major one, experience shows that it is well borne. Recovery is rapid, and the relief is great. Serious complications are rare, provided a sufficiently wide medial pedicle is left intact.

The patient may sit up in bed on the third day. Every other stitch is removed on the fifth day, and by the eighth day all have been removed.

## ANEURYSMS OF THE HAND

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Although false arterial aneurysm due to arterial injury is the most common type of aneurysm of the hand, great interest is aroused in the arteriovenous fistula, which may be either of congenital or of traumatic origin.

Broca, in his work on aneurysms and their treatment, published in 1856, stated that Sennert had been given credit for describing arteriovenous aneurysm but that actually he described only some of the symptoms due to the condition. However, in that detail he was antedated by Antyllus. Hunter<sup>1</sup> presented the first known case and described arteriovenous communication in 1757, before the Medical Society of London. In his case the basilic vein communicated with the humeral artery. In March 1761 Delacoumbe,<sup>2</sup> in France, dissected a spontaneously developing aneurysm of the femoral artery and was surprised to find a vascular connection with the crural vein. This observation of a dissection of an arteriovenous aneurysm was not only the first to be described but, according to Broca, was the earliest record of a spontaneously developing arteriovenous aneurysm.

In an excellent paper on congenital arteriovenous fistulas, Lewis<sup>3</sup> in 1930 collected reports of thirty cases from the literature. In nine of these the condition involved the hand.<sup>4</sup> Since 1928 there have been reported the cases of Horton and Ghormley.<sup>5</sup>

The patient whose case I shall report was admitted to the service of Dr. Clifford Grulee, who asked me to see him.

John D. White, aged 9 years, entered the Presbyterian Hospital, Chicago, on Feb. 11, 1935. About a year before the parents noticed that the middle and ring fingers of the left hand were longer, larger and darker in color than the other fingers of the same hand or those of the right hand. The boy volunteered the information that about the time that these observations were made he had acci-

1. Hunter, William: *M. Obs. Soc. Phys. London* **1**:323, 1757.

2. Delacoumbe: *J. de méd., chir., pharm., Paris* **17**:289, 1762.

3. Lewis, Dean: *Lancet* **2**:621, 1930.

4. Krause: *Arch. f. klin. Chir.* **2**:142, 1862. Gherini: *Gaz. d. hôp.*, 1867. Obalinski and Browicz: *Zentralbl. f. Chir.* **3**:43, 1875. Nicoladoni: *Arch. f. klin. Chir.* **18**:252, 1875. (Nicoladoni reported a second case in 1876.) Sonntag: *Ergebn. d. Chir. u. Orthop.* **11**:99, 1919. Rösler, H.: *Klin. Wchnschr.* **8**:1621 (Aug. 27) 1929. Pemberton, J. de J., and Saint, J. H.: *Surg., Gynec. & Obst.* **46**:470, 1928. Ballin, M.: *J. Michigan M. Soc.* **12**:265, 1913.

5. Horton, B. T., and Ghormley, R. K.: *Proc. Staff Meet., Mayo Clin.* **8**:773 (Dec. 20) 1933.

dentally caught his fingers in the door of a taxicab. The parents had not been told of the accident. The boy was healthy and active. There was no complaint of disability in the use of the hand, of unusual sweating or of pain in the affected hand.

On general examination no abnormalities were noted. The heart was not enlarged; the rate was not increased, and the blood pressure in the right and the left arm was the same. The lower extremities were symmetrical and normal. The left arm was 1.5 cm. longer and slightly larger in circumference than the right. The boy, however, was left-handed. The superficial veins of the left forearm were more prominent than those of the right. The left hand was warmer than the right and was slightly cyanotic. The third and fourth fingers were 1.5 cm. longer than those of the right hand and at least one-third greater in circumference. The digital veins were greatly dilated and showed considerable arterial pulsation. There was a decided capillary pulse in the nails of these fingers. The involved fingers were much warmer than the others, and a definite pulsation and a slight thrill were felt in them. In the palm of the hand, at the base of the third and fourth phalanges, a thrill was palpable, which faded toward the wrist. On auscultation a loud humming continuous bruit, with sharp high-pitched systolic notes occurring synchronously with the heart beat, was heard over the whole hand and fingers, as well as in the forearm to the brachial artery, where it became faint. The sounds were loudest at the base of the fourth phalanx in the palm; I believed this observation to be most important in determining the site of the surgical point of attack on the arteriovenous communication. When a stethoscope was placed on this point and when the ulnar artery in the wrist was compressed, the two bruits almost disappeared, whereas compression of the radial artery affected the noises little. Compression of the brachial artery in the antebrachial fossa, as well as of both radial and ulnar arteries in the wrist, caused complete disappearance of the bruits. In no instance was a bradycardic reaction observed. On compression of the ulnar artery in the wrist, the venous pulsation of the fingers disappeared.

The following observations were apparent from the results of the examinations: that an arteriovenous fistula was present; that it was probably congenital, since the only possible injury that had occurred was in the fingers, while the principal lesion was in the palm; that the site of the arteriovenous communication was probably greatest in the superficial palmar arch and especially at the point where the digital arteries were given off; that a possibility of communication with the deep palmar arch existed, because of the necessity of shutting off both radial and ulnar arteries to stop the bruit entirely.

Dr. C. J. Lundy made injections in order to determine by roentgenographic examination the site of the arteriovenous fistula and whether there were one or more communications. The results were as follows: 1. Skiodan injected into the dorsal vein of the hand failed to show the arterial communication. 2. Skiodan injected into the radial artery at the wrist failed to show the venous communication. 3. Skiodan injected into the ulnar artery indicated that the site of the arteriovenous fistula was probably in the superficial palmar arch. Operation was performed on Feb. 18, 1935, with the patient under ethylene and ether anesthesia.

A Martin bandage was placed on the left arm of the patient, and a longitudinal incision was made parallel to the hypothenar eminence, which divided the annular ligament and exposed the superficial palmar arch. A definite communication between the artery and the veins of the superficial palmar arch

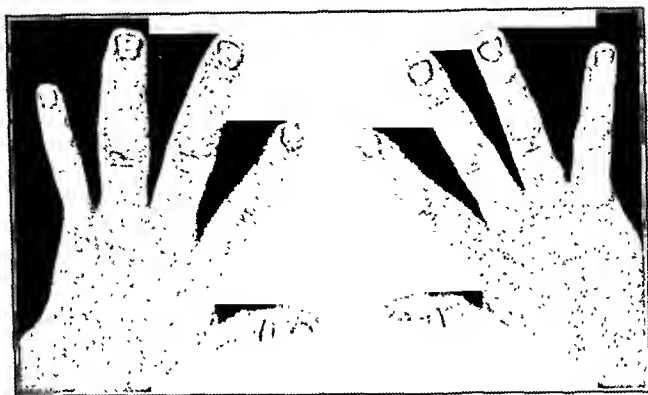


Fig. 1.—Arteriovenous aneurysm of superficial and deep palmar arch, with marked hypertrophy of third and fourth fingers.

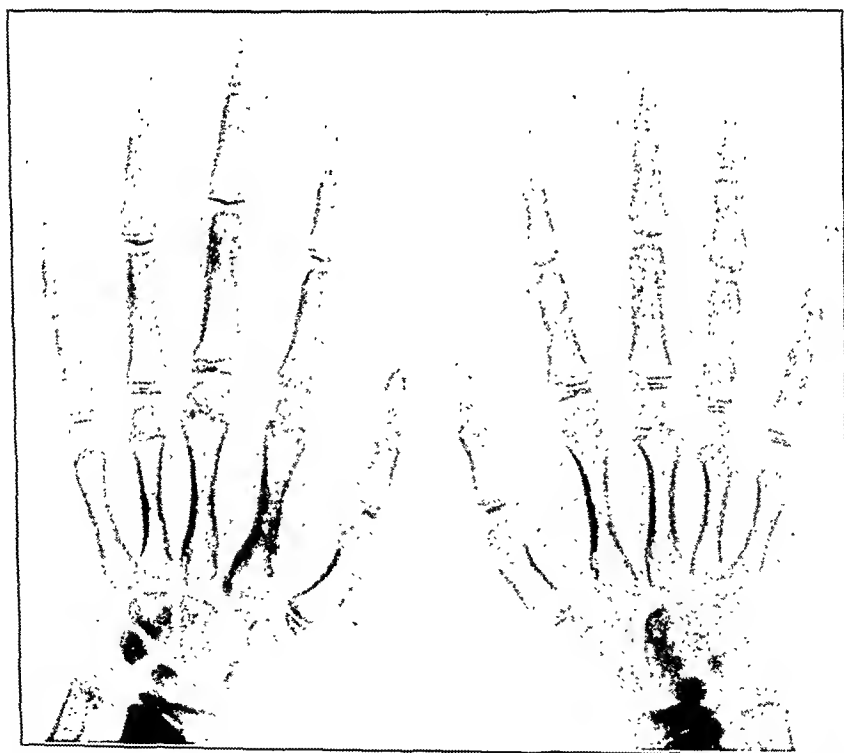


Fig. 2.—Arteriovenous aneurysm of superficial and deep palmar arch, showing overgrowth of phalanges of second, third and fourth fingers.



and a smaller and less definite communication between the superficial palmar arch and the veins of the deep palmar arch were noted. The third and fourth digital veins were greatly dilated. About  $1\frac{1}{2}$  inches (3.8 cm.) of the ulnar artery, including the digital arteries and veins to the third and fourth fingers, was ligated and removed, as well as the dilated communicating branches to the deep palmar arch. The radial artery was not ligated.



Fig. 3.—Arteriovenous aneurysm of superficial and deep palmar arch. Injection of skiodan into ulnar artery shows communication between the superficial palmar arch and the veins to the fourth and fifth fingers.

After the operation the double bruit in the palm and fingers disappeared, and the venous pulse in the veins of the fingers was slight. The third and fourth fingers were less congested and the veins much smaller. Over the radial artery in the wrist, and to lesser degree over the thenar eminence, a double bruit could still be faintly heard if the pressure of the stethoscope belt was exactly right. It was my impression that ligation of the radial artery would eventually be necessary.

An examination of the hand revealed no bruit over the radial or ulnar artery in the wrist or in the palm. The venous pulse had entirely disappeared; the veins in the third and fourth fingers were no longer dilated, and the impression was gained that these fingers were not as prominent as before. Apparently the principal arteriovenous fistula had been removed, although it was thought that smaller ones might be present and might develop later in view of the fact that after the operation a slight double bruit was present in the radial artery and a venous pulse in the fingers was faintly visible.

The most striking aspects of the case are the insidious onset with a doubtful traumatic factor, the considerable hypertrophy of the third and fourth fingers immediately distal to the arteriovenous fistula, the definite venous pulse and capillary pulse, the increased warmth of the hand and the reliability of the stethoscope in determining the point of greatest intensity of the double bruit and, consequently, the site of the arteriovenous fistula. In this case the visualization of the arterial tree and the immediate filling of the veins after the injection of skiodan into the ulnar artery were interesting but did not conclusively define the site of the arteriovenous fistula. In Horton and Ghormley's case the fistula was plainly visualized.

The cardiovascular symptoms are usually absent when the arteriovenous fistula is in the hand or finger, owing to the fact that less blood passes through the fistula. With the type of congenital arteriovenous fistula under consideration, the process often involves the arm secondarily or coincidentally, to a greater or less extent, in which event bradycardia may be present. This fact was noted, as Dean Lewis pointed out, by Nicoladoni and also by Pemberton. In the cases in which extension of the process into the arm has occurred many or all the cardiovascular phenomena carefully tabulated by Lewis and Drury<sup>6</sup> may be present. They are as follows:

1. General arterial pressure (a) Normal systolic pressure and low diastolic pressure, resulting in water-hammer pulse (b) Low systolic pressure, distal to arteriovenous fistula (c) Hill and Rowland's differential pressure sign: difference between systolic pressure of arm and of leg.
2. Capillary pulse
3. Venous pulse
4. Collapsing pulse  
Summit of pulse ill sustained
5. Heart rate slightly increased  
Closure of fistula leads to conspicuous fall of rate below normal reading  
This condition is vagal in origin and is abolished by atropine
6. Output of heart the same
7. Enlargement of the heart due to diminished flow of blood through the coronary vessels

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6. Lewis, T., and Drury, A. N.: *Heart* 10:301, 1923.

Hypertrophy of the extremity complicated by congenital arteriovenous aneurysm has been graphically described by Lewis, Reid<sup>7</sup> and Horton. Broca gave Giralde credit for first describing, in 1854, the lengthening of the limb in these cases. It occurs only in open epiphyses. In Horton's series of twenty-three cases the involved extremity was from 2 to 8 cm. greater in circumference than the normal leg and was from 0.5 to 7 cm. longer.

Of the eleven cases of congenital arteriovenous fistula in which the lesion was principally in the hand or fingers, in eight there was some hypertrophy of the affected extremity, in seven an increase in the length of the whole arm, in three an increase in the size of the whole hand and in two hypertrophy of one or more fingers (fig. 1). Pain was present in only one case. Increase in heat of the affected part was generally observed, and considerable sweating of the hand was noticed in two cases.

Of the eleven cases of primary involvement of the hand, the palm, dorsum and fingers were affected in four, the palm alone in three and the fingers alone in four. In nine of these cases there was some secondary involvement of the arm evidenced either by extension of the arteriovenous fistula into the vessels of the arm (in four cases) or by hypertrophy of the whole extremity with enlargement of the veins of the arm (in four cases).

In only one of these cases was the lesion noticed at birth; in three cases it was observed when the patient was between 1 and 2 years of age, and in the rest of the cases it was first noticed when the patient was between 7 and 20 years of age.

The underlying pathologic changes are not definitely known, but for purposes of clinical discussion it is probably best, as Horton suggested, to include under the head of congenital arteriovenous fistula lesions such as cirroid aneurysm, arteriovenous varix and pulsating venous aneurysm.

In the treatment of these eleven patients varied procedures were used: amputation of the extremity in two cases; amputation of fingers in three cases; ligation of the enlarged veins in one case; compression of the fistula in one case; ligation of the radial artery later followed by ligation of the ulnar artery in one case; ligation of both radial and ulnar arteries at first operation in one case, and ligation of the superficial palmar arch in two cases.

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7. Reid, M. R.: Studies on Abnormal Arteriovenous Communications, Acquired and Congenital: Report of a Series of Cases, *Arch. Surg.* **10**:601 (March) 1925; Abnormal Arteriovenous Communications, Acquired and Congenital: Effects of Abnormal Arteriovenous Communications on Heart, Blood Vessels and Other Structures, *ibid.* **11**:25 (July) 1925; Abnormal Arteriovenous Communications, Acquired and Congenital: Treatment of Abnormal Arteriovenous Communications, *ibid.* **11**:237 (Aug.) 1925.

The ligation of the arteries mainly involved in the lesion effected at least temporary improvement, though the long term result is doubtful. The amputation of the fingers apparently resulted in cure. The ultimate outcome necessarily depends on the extent of the lesion.

#### TRAUMATIC ANEURYSM OF THE HAND

An aneurysm of the hand developing directly as the result of trauma is by far the most common form of the disease and is due almost always to weakening of the arterial wall either by blunt force, which causes a subsequent aneurysmal dilatation, or more commonly by sharp force, such as a wound from a knife or glass, which injures the division of the artery and results in the development of a false aneurysmal sac. A much rarer condition and, in fact, one that it is difficult to find record of in the literature, is arteriovenous aneurysm which develops as the result of direct simultaneous injury of the artery and veins.

Lyle<sup>8</sup> found reports of sixty-one cases of aneurysm of the hand in the literature up to 1924, and Vohlmann<sup>9</sup> in 1930 reported on a series of sixty-seven cases reports of which he collected from the literature from 1922 to 1930. These records are probably not a fair indication of the frequency of the occurrence of the condition, as many of the relatively trivial aneurysms of the hand are not regarded as interesting enough to report. The superficial palmar arch is much more frequently injured than the deep arch; the ratio was 54:8 in Lyle's series. Severe bleeding at the time of injury must be regarded with suspicion. Eighty per cent of the patients had repeated hemorrhages. The aneurysmal sac varied in size from that of a pea to that of an apple and made its appearance from twelve hours to five months after the injury. Almost all the aneurysmal sacs are false, since they are due to lamellation and fibrosis of a hematoma which connects with a defect in the artery. A systolic murmur is heard over the sac, but thrills are rare.

The treatment should be radical; excision of the sac is much better than ligation of the vessels that enter and leave the sac, since failure to effect a cure after the use of the method of ligation has been reported.

The two cases of traumatic aneurysm of the hand to be reported are of interest in that in both the condition involved the radial artery on the dorsum of the hand in the snuff-box space, formed by the extensor pollicis longus and the extensor pollicis brevis muscle, and that in one case both the artery and the vein were involved in the formation of the arteriovenous fistula, which was accompanied by arterial and venous bruits.

8. Lyle, H. M.: *Ann. Surg.* 80:347, 1924.

9. Vohlmann: *Deutsche Ztschr. f. Chir.* 227:151, 1930.

The first case is that of a false aneurysm of the radial artery in the snuff-box space:

A. P. W., a man 20 years old, entered the Presbyterian Hospital on May 28, 1931. About six weeks before entry the patient was in an automobile accident and received a cut from glass over the dorsum of the right hand. Profuse bleeding occurred, which was controlled by two stitches. The wound healed and nothing unusual was noticed at the site of the injury until two weeks before entry, when a swelling developed in the snuff-box space, which gradually increased in size until it was the size of a walnut. There was no pain, but stiffness in the wrist interfered with his work.

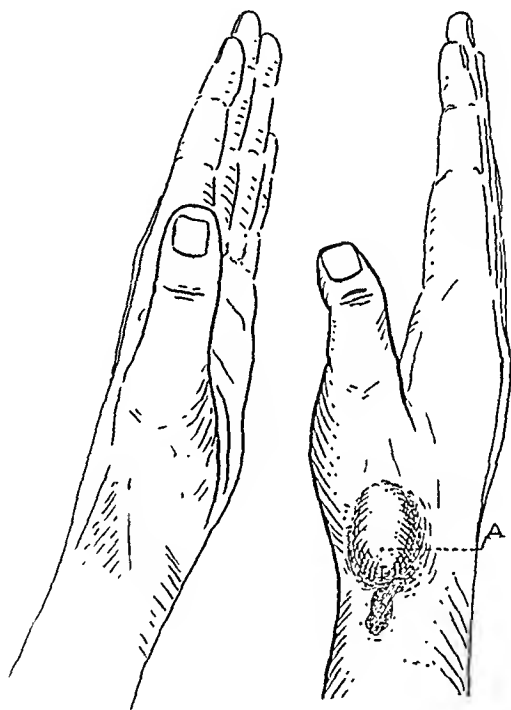


Fig. 4.—Arteriovenous aneurysm of the radial artery and vein, due to injury by shrapnel. *A* indicates the aneurysm in the snuff-box space, filling the shrapnel wound.

The physical examination gave negative results except for the presence of a pulsating tumor over the course of the radial artery on the dorsum of the hand. No bruit was heard over the tumor, nor was there a palpable thrill.

At operation, performed on May 29, 1934, with the patient under ethylene anesthesia, a Martin bandage was used. An incision along the center of the snuff-box space revealed a false aneurysmal sac, made up of a lamellated blood clot, which communicated with an opening in the radial artery about 1.5 mm. in length. The false sac was about 4 by 4 cm. It was removed, and the radial artery was ligated proximally and distally to the opening in it. The vein was not involved. The patient made an uninterrupted recovery, with no motor or sensory disturbances.

The second case is concerned with a war wound that was caused by a small piece of shrapnel entering the snuff-box space of the right hand and that resulted in an arteriovenous aneurysm of the radial artery and vein.

Oscar A. N., a private, was wounded by a small piece of shrapnel that entered the snuff-box space of the right hand on July 15, 1918. Immediately after the injury and to the time of the operation he was unable to extend the distal phalanx of the right thumb, which stood stationary at almost a right angle to the first phalanx. There was, however, no injury to the nerve supply.

Examination on August 11 revealed, in addition to the division of the extensor pollicis longus muscle, a definite thrill over the snuff-box space of the right hand. The thrill was palpable over nearly the entire dorsum of the hand and along the radial artery in the wrist. Auscultation revealed a continuous tremor, punctuated by sharp arterial pulsations which resembled in sound footsteps coming down an empty hall heard over a telephone. Both bruits were heard along the course of the artery in the forearm and along the brachial artery to the axillary space, as well as over the whole hand. There was no venous dilatation or venous pulse in the hand. The arteriovenous bruit was loudest over the snuff-box space. The formation of the tumor was slight.

An operation was performed on August 26, with the patient under ether anesthesia. An incision was made from the base of the first metacarpal of the right hand along the course of the extensor pollicis longus to the middle third of the forearm. Deep in the snuff-box space, embedded in scar tissue, was found a small nodular swelling, 2 by 1 cm., which consisted of a fusion of the radial artery and vein. The tumor was ligated proximally and distally and removed. The divided ends of the extensor pollicis longus muscle were found and sutured together with silk.

On September 18 there was a slight discharge of old blood from the wound. All signs of the aneurysm had disappeared, and the patient was able to move the distal phalanx of the thumb.

In this case of traumatic arteriovenous fistula, scar tissue around the aneurysm prevented the development of a tumor of magnitude, and probably because of it and the recent development of the fistula, sufficient time had not elapsed to allow the veins of the hand to dilate and to show venous pulsation. As in the other case of arteriovenous fistula of the hand, insufficient blood was short-circuited into the venous system and so caused general circulatory disturbances, though in the last case the test for bradycardia was not applied.

# STUDIES IN GASTRO-INTESTINAL MOTILITY

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Of the many technical methods employed in the study of gastro-intestinal motility, none fully escapes criticism. Objections commonly fall into three groups: The animal is, as a rule, anesthetized; a certain amount of trauma is usually entailed, and, finally, the methods of recording are to a certain degree deceptive and misleading in that intestinal activity is either visibly perceived or recorded as a volumetric change in the lumen. In this paper a new method and its application will be presented. While all the objections are not overcome, especially in regard to trauma, the method possesses distinct advantages over any other in use at present. The experiments are conducted on unanesthetized animals; the action of both muscular coats is individually recorded, and, finally, it is possible to apply stimuli to the mucosa in a manner simulating the passage of normal fecal contents.

The paper will be presented in two parts, the first dealing with the method and the preparation and the second with the application of the method to certain physiologic problems.

## METHOD OF INVESTIGATION

The principle involved in this method embodies the exteriorization of a segment of bowel (or stomach) by means of grafting to the abdominal wall.

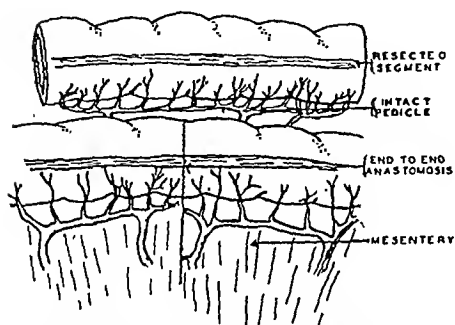
### OPERATIVE PROCEDURE

To prevent contamination with urine, medium-sized female dogs are chosen which appear suitable for training and conditioning. Through a left rectus incision the desired portion of bowel is delivered, and a segment supplied by a single vascular arch is selected. This segment is resected (fig. 1 *A*), leaving the mesentery with its structures intact. An end-to-end anastomosis is performed between the resulting proximal and distal ends to re-establish continuity; the mesenteric defect is closed, and the intestine is dropped back into the abdominal cavity. The abdominal wall is closed around the mesenteric pedicle in layers to the subcutaneous tissues. An area of skin corresponding roughly in

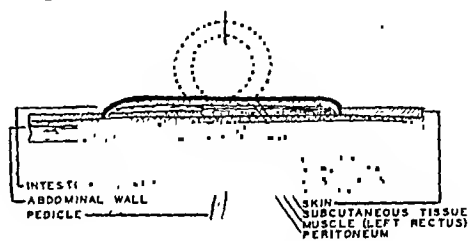
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From the Departments of Surgery and Pharmacology, the Columbia University College of Physicians and Surgeons.

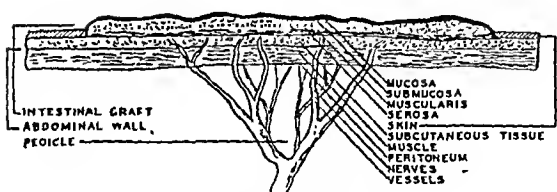
size to the expected graft is then excised, leaving as much of the subcutaneous tissue as possible. The segment of bowel is next opened in a linear direction along the antimesenteric border (fig. 1 C); fecal material is removed, and the mucosal surface is cleansed with saline solution and alcohol. The opened bowel is approximated to the defect in the skin, and the edges are attached to the skin by sutures, which include the full thickness of the graft on one side and the skin and a small amount of subcutaneous tissue on the other. A few interrupted sutures placed beneath the graft serve to approximate the serosa and the subcutaneous tissue and to obliterate dead space.



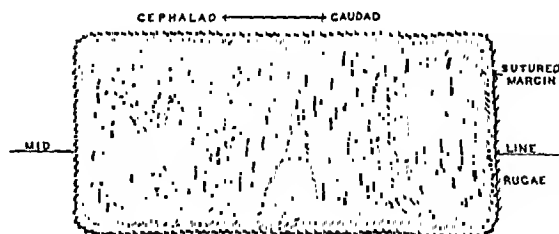
A RESECTION OF INTESTINAL LOOP.



C TRANSPLANTED GRAFT -  
CROSS VIEW.



B TRANSPLANTED GRAFT -  
LATERAL VIEW.



D TRANSPLANTED GRAFT -  
SURFACE VIEW

Fig. 1.—Drawings showing stages of the operative procedure in the grafting of a segment of the intestine.

The procedure for the stomach differs slightly in that a segment is removed from the greater curvature, including a narrow strip from both the anterior and the posterior wall. The pedicle in this case includes branches of the lienal vessel, through which the blood supply is obtained, the pancreaticoduodenal branch being ligated. The gastric defect is closed by inverting and suturing the edges, serosa to serosa. It must be pointed out that in this preparation the branches of the vagus nerve are cut across, and hence the graft does not retain its full nerve supply.

The finished graft (fig. 1 D) is covered with petrolatum gauze, and the surrounding skin is generously smeared with boric acid oint-



ment to prevent irritation and digestion by the intestinal secretions. A pressure dressing is held in place by a light muslin coat. Dressings should be changed every day for a week, after which they may be discarded. It is almost impossible to prevent a certain amount of contamination, and some infection is to be expected. By loose suture of the edges, however, ample drainage is provided, and the graft "takes" and heals by primary intention in the majority of instances. Even when one or more edges separate from the skin, the graft remains viable, and healing, though delayed, is complete.

Training is started immediately after the operation, in order that the animal may be ready for experimentation when healing is complete. This is done by placing the dog on its right side on the apparatus table. Covering with a light sheet helps the conditioning process. Force and even punishment may be necessary to gain cooperation, but with a reward of food the animal soon accepts authority and lies quietly for increasing periods.

The recording apparatus, which is shown in the illustration (fig. 2), employs the use of a modified enterograph consisting of two units. Unit 1 is attached by spring clips to the mucosa at either end of the graft in a longitudinal direction and records the movements of the longitudinal muscle. Unit 2 is superimposed on the first and is attached in the same manner to opposite sides of the graft so as to record the contractions of the circular muscle, all movements being transmitted to a smoked drum on the kymograph by means of levers. Thus, the activity of the individual muscular coats is shown on a smoked drum simultaneously with the time and signal tracings. Gross movements of the animal mar the records, but the minor deviations of the writing levers due to respiratory movements offer no real difficulty in the interpretation of results.

The graft thus prepared is suitable for experimentation for a period of from six to twelve months, depending on the portion of the bowel used and the amount of irritation to which it is subjected. Although the muscle continues to be active and responds to stimulating influences for a longer period, metaplasia, with hardening of the mucosal surface, makes application of the recording clips difficult and vitiates the accurate interpretation of the tracings. It is interesting to note that these changes occur most rapidly in the grafts of the colon, which are rarely useful for more than six months. Sections of the jejunum and ileum, on the other hand, have remained useful for as long as twelve or fifteen months.

#### PATHOLOGIC CHANGES

It is appropriate at this point to speak briefly of the pathologic changes occurring in the grafts, as noted in specimens removed at

various intervals after operation. Sections taken through an entire graft have demonstrated the complete fusion of the serosa to the underlying subcutaneous tissue as well as the fusion of the mucosa to the skin. The muscle coats were hypertrophied, and the submucosa

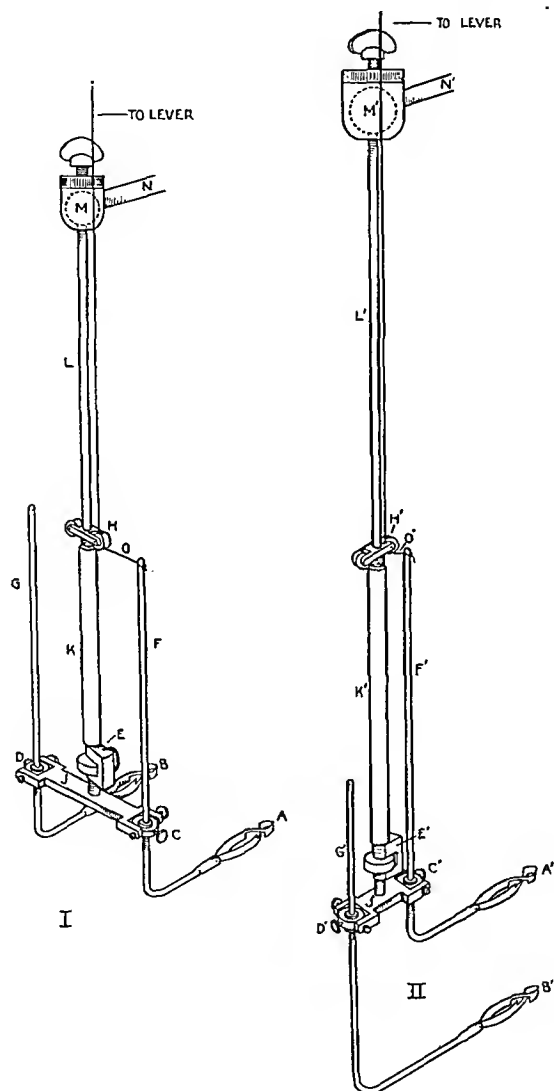


Fig. 2.—Diagram of a modified enterograph, consisting of two units. In unit *I* the spring clips *A* and *B* are attached to the mucosa to be tested. Clip *B*, with its attached lever, *G*, is fixed. Clip *A*, with its rod, *F*, is fastened by a universal joint, *C*, to a bar, *J*, and moves with the changes in distance between *A* and *B*. These movements are transmitted by the string, *O*, through a pulley to the levers of the kymograph. The bar, *J*, rotates on the rod, *L*, which in turn is supported by a ball-and-socket joint, thereby minimizing the deviations of the writing levers in response to the movements of the animal. Unit *II* is superimposed on unit *I* and records in a similar manner the movements of the circular muscle.

was thickened. The muscularis mucosa remained intact unless the graft had been subjected to unusual trauma. The vascularity of the entire preparation, as might be expected, was markedly increased, owing to the development of collateral circulation. The most pronounced changes were observed in the mucosa.

Progressive disintegration of the normal glandular structures was seen in all preparations, depending on the age of the preparation and the amount of trauma. The first noticeable change was wearing off of the tips of the villi, with slight distortion of the superficial portion of the glands. Later the mucosa was often covered by a thin layer of fibrin, which in late stages became organized. Shutting off the openings of the crypts sometimes impeded the escape of secretory products, with subsequent cystic dilatation at the bases. Of greatest importance

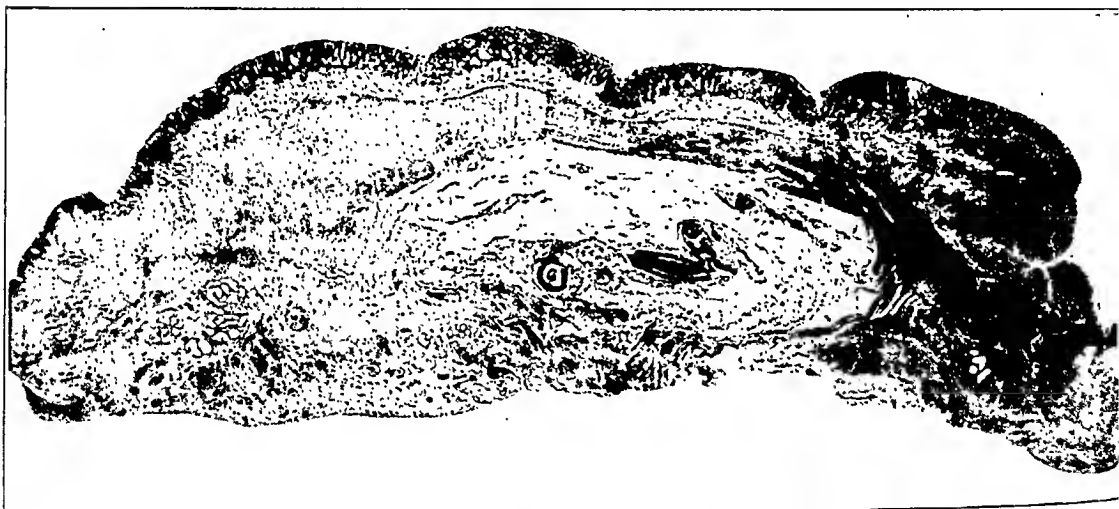


Fig. 3.—Low power photomicrograph of a section taken transversely through the midportion of a graft from the ileum at the end of five months. The points of contact with the skin, the hypertrophy of the muscle and the relatively normal appearance of the mucosa are evident. The light area in the center indicates properitoneal fat, and in it can be seen the vessels of the pedicle.

was the histologic evidence of regeneration of the glandular epithelium, demonstrating that the mucosa is not devitalized by transplantation to a strange environment (figs. 3 and 4).

It is of interest to note that occasionally, but not invariably, peninsulas of squamous epithelium grow out from the edges of the skin, forming almost isolated islands as large as 1 cm. in diameter. That these occur in areas denuded of mucosal epithelium is suggested by the absence of glandular structures beneath them. The remarkable regenerative powers of the grafted portion of bowel were illustrated

in an animal in which a newly prepared flap was almost chewed off. The defect closed in rapidly by a fungating mass of granulation tissue, which later retracted to the size and thickness of the original graft. The mucosal epithelium was not replaced, however, and six months

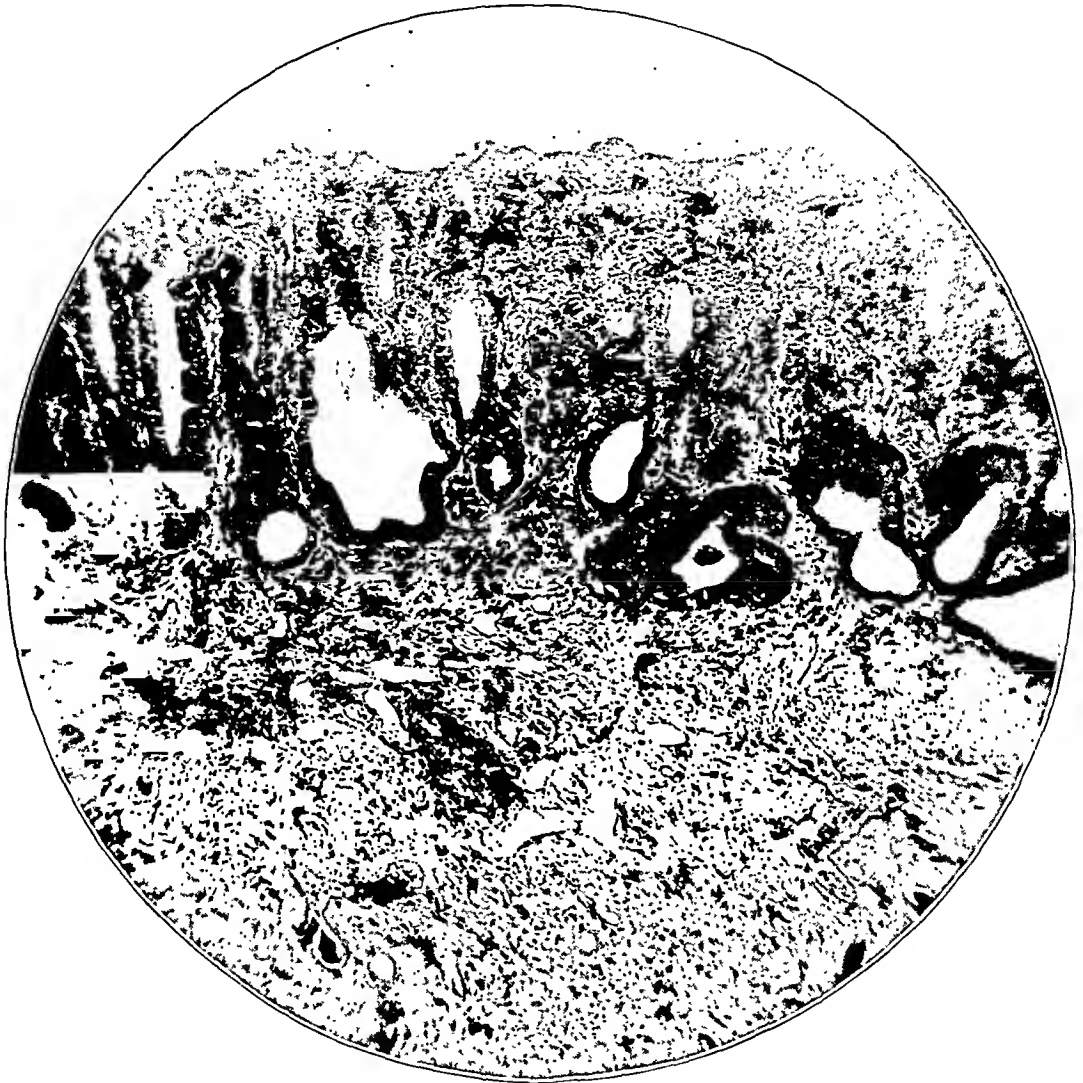


Fig. 4.—High power photomicrograph of the section shown in figure 3. The superficial fusion of the tips of the villi, with beginning disintegration, the dilatation of the bases, the beginning disruption of the muscularis mucosa and the hypertrophy of the submucosa are apparent.

later, when the graft was removed, it presented the histologic appearance of the base of a chronic ulcer, with marked fibrosis and cellular infiltration.

## BASIC REACTION

Before one proceeds to the description of specific experimental work, it is necessary to establish what may be termed the basic reaction of the graft under the existing conditions. A muscular response is invariably noted immediately after attachment of the clips, due no doubt to the irritation of attachment. This activity assumes the form of a series of reciprocal contractions of each muscle coat, lasting from one to two minutes but rarely constant either in magnitude or in duration. It is at this point, however, that a significant fact is noted. These contractions invariably occur at intervals of constant frequency. In the small intestine the interval is from four and a half to five seconds, while in the colon it is between fifteen and sixteen seconds. This is designated as the oscillatory frequency of the intestinal musculature, and it remains fairly constant, irrespective of the type of stimulation employed to incite muscular activity (to be described later).

Once the effect of attaching the clips has passed, the recording levers reach a base line. This represents the basic intrinsic activity and differs according to the portion of bowel tested. Thus, while no portion demonstrated active motion during the fasting state, after the ingestion of food there was observed the institution of an inconstant cycle of activity. In the jejunum and ileum this consisted of a series of minor contractions of both muscle coats at the established oscillatory frequency (from four and one-half to five seconds). These minor contractions appeared in definite cycles of magnitude, which recurred at intervals of from five to eight minutes. In the colon two important differences were noted. Although the oscillatory frequency (from fifteen to sixteen seconds) was maintained, there were no definite cycles, and the individual contractions were of less magnitude. While it is difficult to determine which muscle coat is primarily affected in the food reflex, the circular muscle appears to predominate.

To summarize briefly, two important facts are established: 1. All intestinal musculature exhibits minor rhythmic contractions of a definite oscillatory frequency in addition to the changes in tone, or major contractions, regardless of the type of stimulus producing the activity. 2. A muscular reflex is instigated by the ingestion of food into the stomach, which is manifested in all parts of the bowel. The second phenomenon coincides with the findings of other investigators and represents the graphic proof of the so-called food reflex, a physiologic fact illustrated by the desire to defecate after partaking of food. That this is a central or spinal cord reflex is demonstrated by its absence after severance of the mesenteric pedicle with its nerve supply. It is to be emphasized, however, that the preceding statement applies only to the intestinal tract, as neither type of contraction has been observed in the stomach preparations tested.

## APPLICATION OF THE METHOD

## MECHANICAL STIMULATION

It was found, quite by accident it must be confessed, that light stimulation of the mucosa produced a definite and constant response of the intestinal musculature. With the use of a standardized stimulus of ten strokes with a blunt teasing needle administered for a period of from eight to ten seconds, attempts were made to analyze the intestinal response. Thus, it was found that with the recording clips attached at opposite sides and ends of the graft, as already described, stimuli applied throughout its length near the center produced strong contrac-

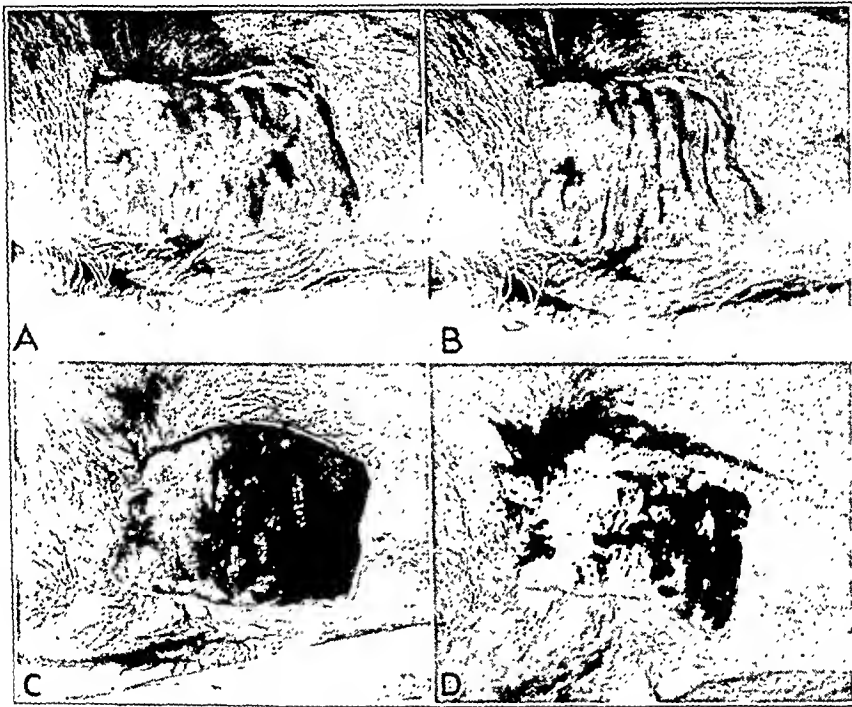


Fig. 5.—Photographs showing stages of contraction in the graft from the colon. *A* represents the normal graft; *B*, contraction of the longitudinal muscle after longitudinal stimulation; *C*, contraction of the proximal half of the graft only after transverse stimulation near its center, and *D*, contraction of the circular muscle throughout almost the entire graft after circular stimulation at the distal end.

tion of the longitudinal muscle, with coincident relaxation of the circular muscle. This was followed shortly by contraction of the circular muscle and relaxation of the longitudinal muscle. If the stimuli were then applied transversely between the clips, a definite change of reaction was noted. The initial contraction of the longitudinal muscle was present but was of less magnitude, while the initial contraction of the circular muscle was stronger and occurred more quickly after the initial application of the stimulus (figs. 5 and 6). This is explained

on the basis of the transmission of nerve impulses to more sensory end-organs of the longitudinal muscle coat in the first instance and to more end-organs of the circular muscle coat in the second. This, in general, is the typical response of all portions of the intestinal tract. There are, however, certain characteristic differences in the types of contraction elicited in different parts of the intestine, which are manifested chiefly in the predominance of the muscle coat involved and the time relations of stimulation and contraction.

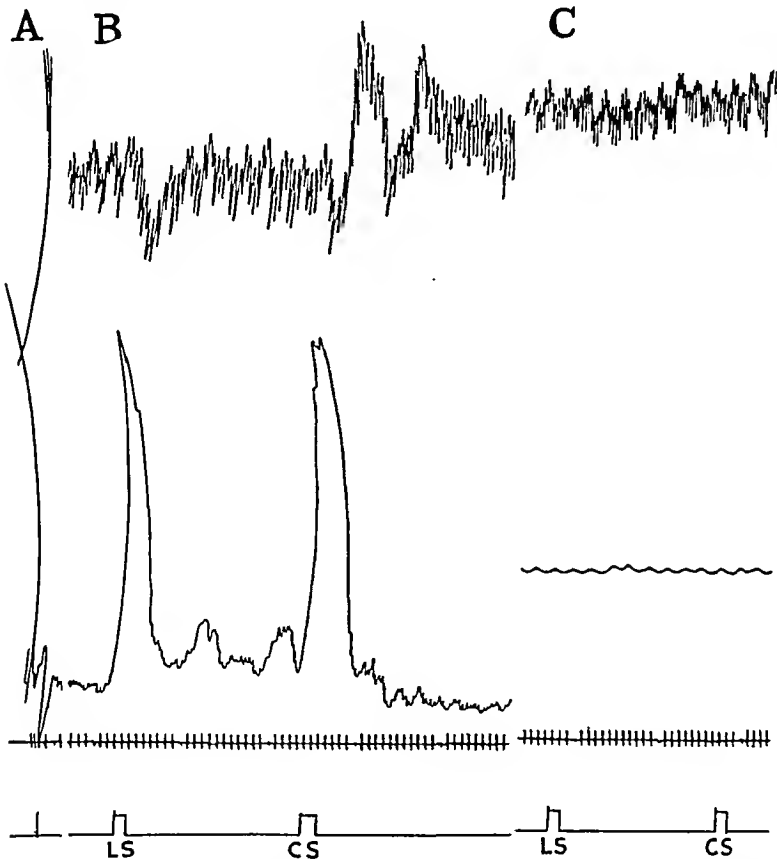


Fig. 6.—Tracing on a smoked drum of a typical contraction after longitudinal (LS) and circular (CS) stimulations. *A* shows the tracing by which the contractions are measured for their time relationships; *B*, the response of the normal graft to both types of stimuli, with the minor rhythmic deviations of the circular muscle at intervals of approximately fifteen seconds, (the animal had been fed one-half hour before the tracing was taken), and *C*, the response after atropine had been injected. The food reflex (minor rhythmic contractions) persists, but all response to mechanical stimulation has been lost.

In none of the stomach grafts observed was typical muscular activity elicited by any type of stimulation. The reason for this cannot be given at present, but the fact that the branches of the vagus nerve were severed may be responsible in part.

In the jejunum the contraction of the longitudinal muscle was of moderate magnitude after longitudinal stroking and of minimal magnitude or even absent after stimulation in the transverse direction. The contractions of the circular muscle predominated after both types of stimuli, the only differences being in the abruptness of the contraction and its duration. Both the major contractions were accompanied by minor rhythmic oscillations of the established frequency. In the ileum the contractions of both coats were of less magnitude, appeared to be more sluggish and were rarely accompanied by minor oscillations. The contraction of longitudinal muscle invariably predominated in the colon, but the contractions were smaller after circular than after longitudinal stroking. Activity of the circular muscle was minimal or sometimes absent after longitudinal stimulation and constant and strong after cir-

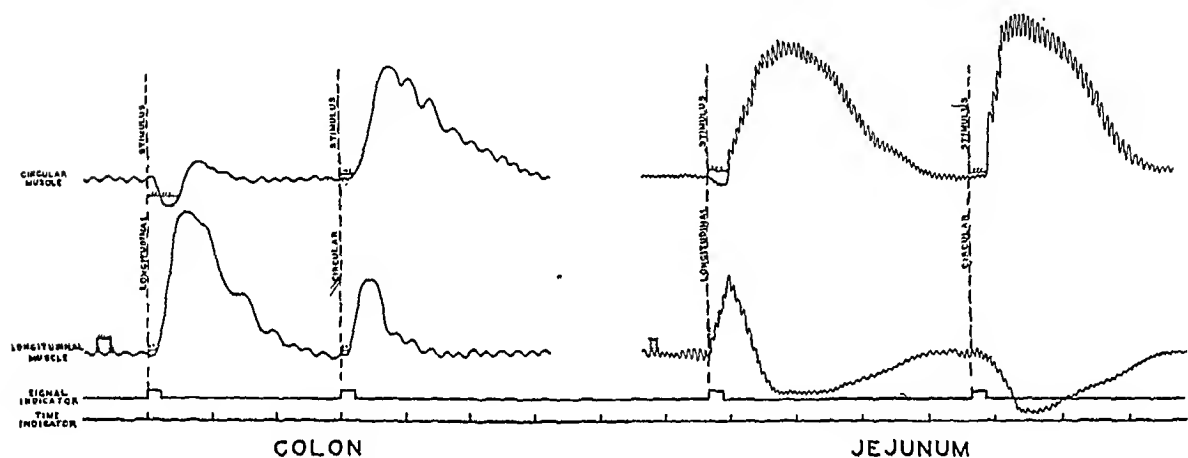


Fig. 7.—Diagrammatic reproduction of typical forms of contraction in the colon and in the jejunum. The preponderance of contractions of the longitudinal muscle in the colon and that of the contractions of the circular muscle in the jejunum are evident. After longitudinal stimulation of the colon the circular muscle reacts little if at all, while the same is true of the longitudinal muscle of the jejunum after circular stimulation. The minor rhythmic oscillations of the jejunal musculature are more exaggerated and rapid. In this diagram and in the diagram shown in figure 9, time is indicated in units of five seconds.

cular stimulation. In figure 7 are illustrated graphically the types of response seen in the jejunum and the colon.

The time relations of contraction and stimulation are most clearly shown in table 1.

The table designates the time, expressed in seconds, elapsing between the initial application of the stimulus and the various phases of the muscular movement, as shown in the column at the left. For the sake of clarity the term latent period is used to designate the time between the stimulus and the initial contraction. Thus, it is seen that in the jejunum the longitudinal muscle reacts more quickly than in other por-



tions of the bowel. The direction of stimulation appears to exert little effect on the latent period, but the duration of the contraction is maintained longer after longitudinal stimulation. The circular muscle reacts more slowly than the longitudinal muscle, but it reacts more quickly after circular than after longitudinal stimulation. The contraction is maintained no longer, however. In the ileum both the muscle coats respond more slowly than in the jejunum, but again the circular coat responds more quickly after circular than after longitudinal stimulation. In the colon the activity of the longitudinal muscle appears more slowly than in the jejunum and faster than in the ileum. The circular muscle reacts more quickly in the colon than in either of the

TABLE 1.—*Time Relations of Contraction and Stimulation\**

Phase	Longitudinal Stimulation*		Circular Stimulation†	
	Longitudinal Muscle	Circular Muscle	Longitudinal Muscle	Circular Muscle
Jejunum				
Latent period.....	2.5	19.8	3.0	13.8
Height of contraction.....	9.0	36.7	7.5	24.2
Beginning of descent.....	22.7	105.4	22.3	65.4
Base line.....	44.1	133.5	36.5	118.2
Ileum				
Latent period.....	6.9	25.3	6.1	16.3
Height of contraction.....	13.5	52.7	21.2	31.9
Beginning of descent.....	31.4	80.2	44.6	63.8
Base line.....	54.4	115.7	59.6	100.2
Colon				
Latent period.....	4.0	14.8	4.9	8.9
Height of contraction.....	12.0	23.3	11.2	19.3
Beginning of descent.....	24.8	47.0	29.6	42.4
Base line.....	49.4	62.3	39.2	65.2

\* The time relations are measured in seconds.

† The terms "longitudinal stimulation" and "circular stimulation" as used here and elsewhere in the text refer to the direction in which the bowel was stroked and not to stimulation of the individual muscle coat.

other bowel preparations, and again there is the quickened response after circular stimulation.

Certain features of the preceding description merit further discussion. The relaxation of the circular muscle coincidental to the contraction of the longitudinal muscle may represent either an active or a secondary inhibition. Although definite proof is lacking, associated evidence favors the latter surmise, namely, that the relaxation is a mechanical phenomenon caused directly by the contraction of longitudinal muscle. It is comparable to the stretching of a rectangular sheet of rubber dam in that as the length is increased the width is correspondingly decreased in order to maintain the same surface area. That this is true is suggested by the fact that the inhibition always follows the contraction by a short interval and returns to the base normal with the cessation of the contraction. Further, in an area in which the

circular but not the longitudinal muscle is sensitive to a localized stimulus, there is no inhibition of the contraction of circular muscle after stimulation.

Muscular fatigue may be shown by application of repeated consecutive stimuli. When this is carried out, the initial contraction of longitudinal muscle is similar to that in the instances already described, but is maintained longer. When the circular fibers begin to contract, the longitudinal muscle is partially inhibited (as may be expected in view of the aforementioned principle). It does not return to its normal state, however, and both coats maintain a moderate degree of tonus as long as twenty or thirty minutes, after which the muscle appears to have temporarily lost its contractility. This returns in a short time, however, and contractions of the same magnitude as those obtained before fatigue may again be elicited. If the muscle is allowed to return to its normal state of tone each time before the new stimulus is applied and the process is repeated, contractility is not lost, although the contractions may become weaker.

On review of the aforementioned facts, one immediately considers the location of the reflex arcs responsible for these phenomena. That the reflex is myenteric or local has been shown in several ways. First, and most conclusively, the activity is in no way diminished or altered by section of the mesenteric pedicle with its blood and nerve supply. Second, topical application of cocaine completely abolishes the receptivity of the mucosa to the stimulus at any given point but does not alter the muscular response at that point to a stimulus applied outside the cocainized area in an active zone of stimulation. Third, the subcutaneous injection of atropine abolishes all response to stimulation within a few minutes. Fourth, a double graft has been prepared in which the continuity of the resected segment was broken by section and then reestablished by suture. Stimulation in any portion of one graft elicited no response in the other. Finally, it has been shown that the intestine retains some degree of activity when entirely removed from the body. The intestine of the embryonic rat exhibits a moderate degree of peristaltic activity when kept in Ringer's solution for several days. Further, grafts removed from experimental animals have retained muscular response to pinching of the mucosa as long as one hour after removal if placed in warm saline solution.

To summarize briefly, from a study of the types of contraction and the speeds with which they respond to stimulation, the following concepts of the activity of different portions of the bowel are formed: The jejunum is most irritable, as shown by its quicker response to stimulation and the persistence of minor rhythmic contractions at a definite oscillatory frequency. Further, the contractions of the circular muscle are predominant. Both these facts are in keeping with the function of

the jejunum in the propulsion of semifluid fecal contents. The ileum is more sluggish; its contractions exhibit no rhythmic oscillations, and the changes of both the longitudinal and the circular muscle coat are of less magnitude. The colon is by far the most powerful, as demonstrated by the greater magnitude of both types of contraction, and the contractions of either muscle coat may predominate, depending on the direction of the stimulus, a form of activity to be expected from the function possessed by the colon of manipulating solid fecal material. Finally, it has been shown beyond doubt that this activity results from a myenteric reflex.

#### LOCATION OF STIMULI

*The Law of the Intestine.*—During the course of the previous experiments it was noted that transverse stimulation proximal to the point of attachment of the recording clips produced no recorded contraction, that is, no contraction between the clips, although there was visible contraction of the circular muscle proximal to the point of stimulation. Attempts were then made to localize the areas of receptivity to stimuli or, in other words, to determine in what portions of the graft movements could be elicited by stimulation at any given point. By the simple expedient of shifting the recording clips and using one unit at a time, it was possible to demonstrate that either muscle coat responds only to stimuli within a definite zone. This area is termed the irritation zone.

A. Localization of Stimuli Necessary to Produce Contraction of the Longitudinal Muscle: The points of stimulation are best shown by means of the upper diagram in figure 8. Circles indicate attachments of the clips in different positions, while the connecting lines show the position of the stimuli. *A*, *B*, *C* and *D* represent the positions of the recording clips, while *C*, *L* and *R* indicate the center and the left and right portions, respectively, of the graft. With the clips at *A* and *B*, stimuli were applied between *A* and *B*, *B* and *C* and *C* and *D*, not only at the center of the graft but at each margin. Thus, for each position of the clips stimuli were applied at nine points. The procedure was then repeated with the clips at *B* and *C* and finally at *C* and *D*. The results are shown in table 2 and graphically in figure 9.

It is therefore obvious that a stimulus applied to the intestinal mucosa below, or distal to, the point which is recorded elicits no contraction of the longitudinal muscle above the point of stimulation. Stimulation at or above the point of record produces strong contractions at and below the area of stimulation which decrease in magnitude as the distance from this area increases. In the three portions of the table it is shown that stimuli applied along the longitudinal plane in which the recording clips are attached produce contraction only if they

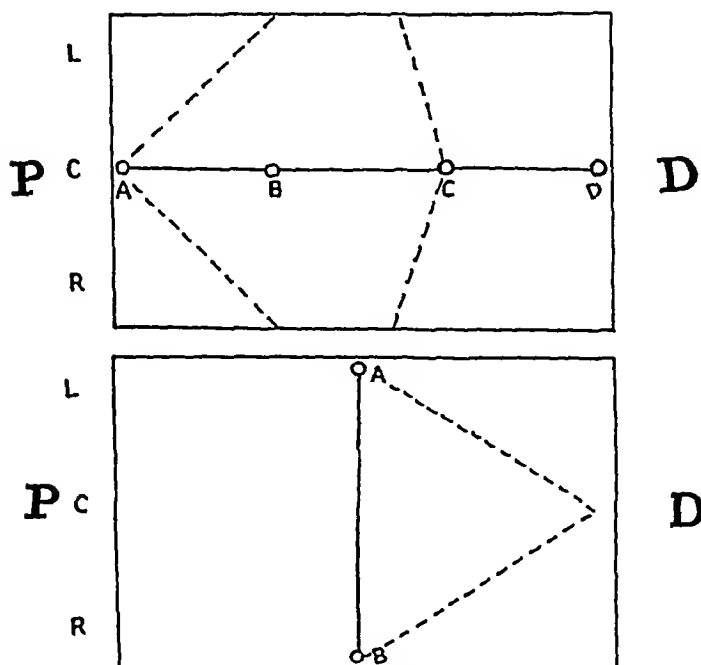


Fig. 8.—Schematic representation of the graft taken from the colon. *P* represents the proximal end; *D*, the distal end; *R*, the right side; *L*, the left side and *C*, the center. The solid line with circles represent the attachment of the clips of the recording instrument. Further details are given in the text. With the clips attached at *B* and *C*, as shown in the upper diagram, stimuli within the area enclosed by the broken lines are effective in eliciting a contraction of the longitudinal muscle. With the clips at *A* and *B*, as shown in the lower diagram, stimuli within the area of the isosceles triangle with the base *A-B* and the broken lines are effective in eliciting a contraction of the circular muscle between *A* and *B*.

TABLE 2.—Effect on Contractions of the Longitudinal Muscle Coat of an Intestinal Graft of Stimulation of Various Points of the Mucosa (Fig. 8)

Position of Stimulus	Effect	Position of Stimulus	Effect	Position of Stimulus	Effect
Recording Clips Attached at A and B					
AB-L	Moderate contraction	BC-L	No contraction	CD-L	No contraction
AB-O	Strong contraction	BC-O	No contraction	CD-C	No contraction
AB-R	Moderate contraction	BC-R	No contraction	CD-R	No contraction
Recording Clips Attached at B and C					
AB-L	Moderate contraction	BC-L	Moderate contraction	CD-L	No contraction
AB-O	Strong contraction	BC-O	Strong contraction	CD-C	No contraction
AB-R	Moderate contraction	BC-R	Moderate contraction	CD-R	No contraction
Recording Clips Attached at C and D					
AB-L	Weak contraction	BC-L	Moderate contraction	CD-L	Moderate contraction
AB-O	Moderate contraction	BC-O	Strong contraction	CD-C	Strong contraction
AB-R	Weak contraction	BC-R	Moderate contraction	CD-R	Moderate contraction

are applied between the clips or proximal to them. When the stimulus is applied lateral to the plane of the clips, the motor response diminishes rather rapidly. When it is applied proximally, the stimulus is effective for a distance of from 4 to 6 cm. When applied laterally it is effective only within 2 or 3 cm. This reflex action becomes intelligible on the assumption that there are sensory and motor nerve connections which run distal to the point of stimulation. Apparently the mucosa has no nerve connection with the longitudinal muscle above its own level.

To summarize, stimulation of the mucosa causes contraction of the longitudinal muscle at and below the point of stimulation, but none above. With a linear stimulus the area of contraction may be represented by an isosceles triangle (fig. 8). Conversely, a given area of the intestine contracts when stimuli are applied above it. Such a

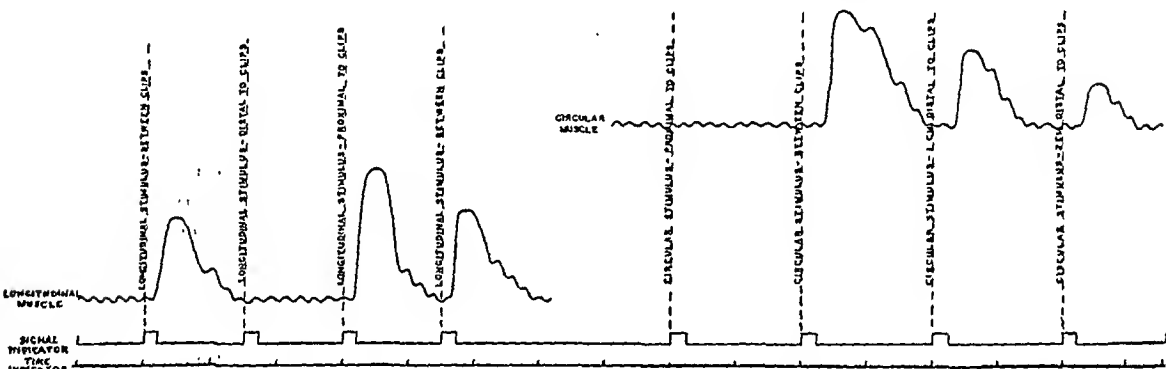


Fig. 9.—Results of stimulation of the colon at different positions on the contraction of the longitudinal and the circular muscle. Stimulation of the distal part produces no contraction of the longitudinal muscle, while stimulation of the proximal portion produces no contraction of the circular muscle.

stimulus acting alone would cause an increase in the diameter of the intestinal lumen below the point of stimulation.

**B. Localization of Stimuli Necessary to Produce Contraction of the Circular Muscle:** The lower diagram in figure 8 shows the position of the clips on the graft and the points of stimulation. The clips were attached at *A* and *B*. Stimuli were applied at points 2 and 4 cm. on either side of the center. The results are shown in table 3 and graphically in figure 9.

It is at once obvious that the circular muscle responds to stimuli in a manner different from that of the longitudinal muscle. All stimuli proximal to the clips are incapable of eliciting contraction between the clips. Stimulation between or distal to the clips, on the other hand, elicits contraction which varies inversely as the distance from the point of stimulation. When stroke stimuli are applied trans-

versely, both muscle coats respond with contraction, with that of the circular muscle predominant, as already described. It may therefore be assumed that there are sensory and motor nerve connections which run proximal to the point of stimulation. The mucosa appears to have no nerve connections with the circular muscle below its own level.

The characteristics just described have been noted in all three portions of the bowel tested, although not as distinctly in the jejunum and ileum. An interesting variation was noted in the jejunum. While there was no immediate contraction of the circular muscle distal to the point of stimulation, evidence of activity could be seen several seconds later. If watched closely this contraction could be seen to pass downward from the initial contraction in the manner of a peristaltic wave. If the distance was measured between the point of stimulation and the recording clips when placed distally, the speed of the wave could

TABLE 3.—*Effect on Contraction of the Circular Muscle of an Intestinal Graft of Stimulation of Various Points of the Mucosa (Fig. 8)*

Position of Stimulus	Left	Center	Right
Recording Clips Attached at A and B			
Proximal to clips			
4 cm.	No contraction	No contraction	No contraction
2 cm.	No contraction	No contraction	No contraction
Between clips	Strong contraction	Strong contraction	Strong contraction
Distal to clips			
2 cm.	Weak contraction	Strong contraction	Weak contraction
4 cm.	No contraction	Weak contraction	No contraction

be determined. It was found to move at the rate of approximately 1 cm. in twenty seconds.

#### COMMENT

The results obtained in these experiments and the work by one of us (M. G. M.)<sup>1</sup> on pithed cats show beyond any shadow of doubt that stimulation of the vagus nerve or mucosal irritation elicits contraction first of the longitudinal and then of the circular muscle. The result of such a mechanism is to increase the lumen of the intestine and then to decrease or obliterate it. These experiments offer no suggestion that either muscle coat is at any time actively inhibited by mucosal stimulation. If a balloon system is used as a recorder, the effect, i. e., the contraction of the longitudinal muscle below the point of stimulation followed by spasm of the circular muscle above, may be interpreted as inhibition (increase in volume of the intestinal lumen) followed by stimulation. The fallacy of such an observation has already been pointed out.

1. Mulinos, M. G.: Proc. Soc. Exper. Biol. & Med. 29:186, 1931.

The results obtained by a more careful study of the locus of stimulation and the region of response point definitely to the existence of a myenteric reflex. The sequence of events is somewhat as follows: A stimulus (bolus) at any point along the intestine elicits contraction of the longitudinal muscle at and below that point. The lumen is enlarged to permit reception of the bolus. A few seconds later there is contraction of the circular muscle at and above the point. The lumen is thereby constricted, forcing the bolus onward. These phenomena are graphically illustrated in figure 10.

The phenomenon is a true reflex, for it is abolished both by cocainization and the injection of atropine sulfate systemically. It is a true myenteric reflex, for it does not depend on any connection with the paravertebral sympathetic ganglions. All that can be said at present is that this myenteric reflex occurs in intact, unanesthetized dogs. No denervation or purging is necessary (Bayliss and Starling,<sup>2</sup> Cannon<sup>3</sup> and Alvarez<sup>4</sup>). It is possible that the localized stimulus if continued

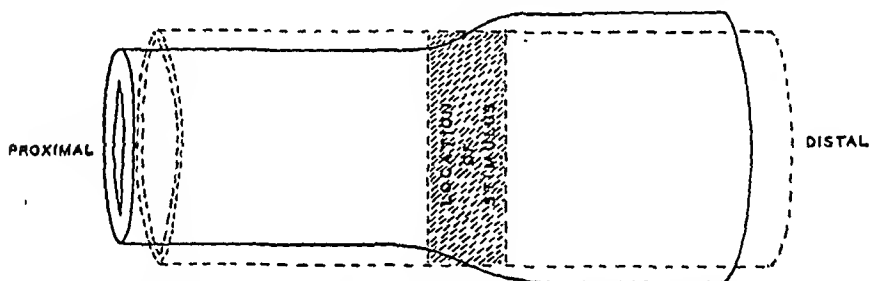


Fig. 10.—Graphic representation of the law of the intestine: When the stimulus (bolus) is applied in the shaded area, the longitudinal muscle contracts proximal to the point of stimulation and the circular muscle distal to the point, with the results explained in the text.

downward along the intestinal mucosa would result in a chain reflex, giving the appearance of peristalsis. No such studies have as yet been made.

It has already been mentioned that the mucosa is functionally connected with the two muscular coats in a characteristic manner. Sensory nerves (afferent) connect the mucosa with the longitudinal muscle at and below its own level and with the circular muscle at and above the same level. Further, impulses to the longitudinal muscle become manifest more quickly than impulses to the circular muscle. It is impossible to say at this time whether the difference in the rate of response is to

2. Bayliss, W. M., and Starling, E. H.: *J. Physiol.* **24**:90, 1899.

3. Cannon, W. B.: *Am. J. Physiol.* **30**:114, 1912.

4. Alvarez, W. C., and Mahoney, L. J.: *Am. J. Physiol.* **69**:211, 1924. Alvarez, W. C., and Starkweather, E.: *ibid.* **47**:293, 1918.

be found in the afferent fibers of the nerves or in the circularly arranged muscle fibers. It may be that in the case of the longitudinal muscle fibers the afferent nerves have their endings and, presumably, the source of acetylcholine or other such hormones (Mulinos, 1929) very near the parasympathetic myoneural junctions of the muscle. The quickness of response is, then, a function of the rate of diffusion of the *Vagusstoffe* into the cell. On the contrary, the smooth muscle cells of the circular coat may lie at a greater distance from the nerve endings, giving a response which is slower than that of the longitudinal muscle by the time necessary for diffusion into the cell. This same delay in transit exposes the acetylcholine to the destructive action of the esterase, so that less of the drug reaches the cell. Such a concept may explain the observation that longitudinal stimulation of the mucosa of the colon rarely elicits contraction of the circular muscle, while transverse stimulation produces contractions in both coats. The intestinal mucosa may be pictured as made up of a mosaic of sensory nerve receptors. These are arranged in rows of pairs, one member of each pair to the circular muscle and the other, to the longitudinal muscle. On longitudinal stimulation a large number of pairs are stimulated, but only a few of the endings send fibers to any one set of circular muscle fibers. The little acetylcholine which is liberated near the circular muscle is destroyed by the esterase before it can reach the cell, and there is no contraction. When the stimulus is applied transversely, there is much more response because the number of impulses to the muscle is many times the number arising from longitudinal stroking. The longitudinal muscle fibers respond to both types of stimulation because they are situated nearer their corresponding nerve endings. We believe that the sensory elements of the myenteric reflex persist after the graft has been separated from the central nervous system.

#### ACTION OF DRUGS

The next phase of experimentation is concerned with the action of certain drugs on the exteriorized bowel. While the work is not complete at present, several interesting results have been obtained. To avoid ambiguity these will be discussed in groups.

*Morphine Group.*—That morphine causes strong contraction with "splinting" of the bowel is commonly accepted. By means of the exteriorized graft the mode of its action can be easily demonstrated. Thus, it was seen that when morphine was injected subcutaneously there followed after a latent period of from thirty seconds to two minutes a gradual spastic contraction of the circular muscle, which usually reached its height after from one or two minutes and was maintained for more than an hour. This effect was constant but varied in degree



at different times and in different animals. Coincident to the contraction of the circular muscle the longitudinal muscle was inhibited, the recording lever falling far below the base line and remaining there until after the contraction of the circular muscle had ended. If the mucosa was stimulated by mechanical means during this period there was no change of tone. There was, however, an exaggerated excursion of the minor rhythmic contractions coincident to the spastic change, which maintained the established oscillatory frequency.

A mixture of the hydrochlorides of the opium alkaloids similarly injected in proportionate doses produced a similar result. Papaverine, on the other hand, produced no effect, regardless of the dose administered. Other derivatives of opium have not been tested.

*Pitressin Group.*—This group includes a number of drugs which are not necessarily related to the extracts of the pituitary gland but which are used clinically for the activation of peristalsis in the presence of paralytic ileus.

No constant effect could be demonstrated by the subcutaneous or intramuscular injection of pitressin, in doses as great as 2 ampules at the time. In one or two experiments strong contraction of the longitudinal muscle was noted, with coincident inhibition of the circular muscle, but since this could not be repeated in subsequent tests its authenticity is to be doubted. If, however, pitressin was injected during the height of a morphine spasm, the circular muscle was invariably released from the effects of the morphine spasm within a few minutes (fig. 11).

Intramuscular injections of solution of posterior pituitary likewise produced no demonstrable changes. Peristaltine, a drug containing the active principle of cascara sagrada, produced no constant or conclusive reaction, nor did a German preparation of an extract of the spleen. Physostigmine salicylate caused an increase in the activity of both muscle coats, resulting in coincidental contractions of moderate magnitude of the longitudinal and the circular muscle, with a slight increase in tone. The activity was greatest between five and twenty-five minutes after injection, but it was not constant or persistent. Acetylcholine likewise resulted in a series of coincident contractions, which lasted for about fifteen minutes and were accompanied by a general increase in irritability to mechanical stimulation.

*Other Drugs.*—Epinephrine injected intravenously in small doses produced an inconstant major contraction of the longitudinal muscle, beginning from one to two minutes after injection. Larger doses produced subsequent strong and well sustained contraction of the circular muscle. Blanching of the mucosa usually followed the injection of even minute doses in about twenty seconds. Ephedrine, on the other

hand, caused no conclusive activity. Histamine, when injected intramuscularly, produced an increase in the activity of both coats, especially the circular. Like physostigmine salicylate, it increased the irritability of the mucosa to mechanical stimulation.

The effects of atropine have already been mentioned. While it caused no muscular activity in itself, it inhibited all reaction to mechanical stimulation. It did not, however, affect the spastic contraction brought on by morphine, whether administered before or after the latter drug. Cocaine applied topically destroyed the receptivity to mechanical stimuli at the point applied but did not prevent contraction of the muscle at that point if the stimulus was applied elsewhere in a zone sensitive to irritation. Beginning about one minute after application, however, there was marked contraction of the circular muscle, which reached its greatest magnitude about three minutes later and was main-

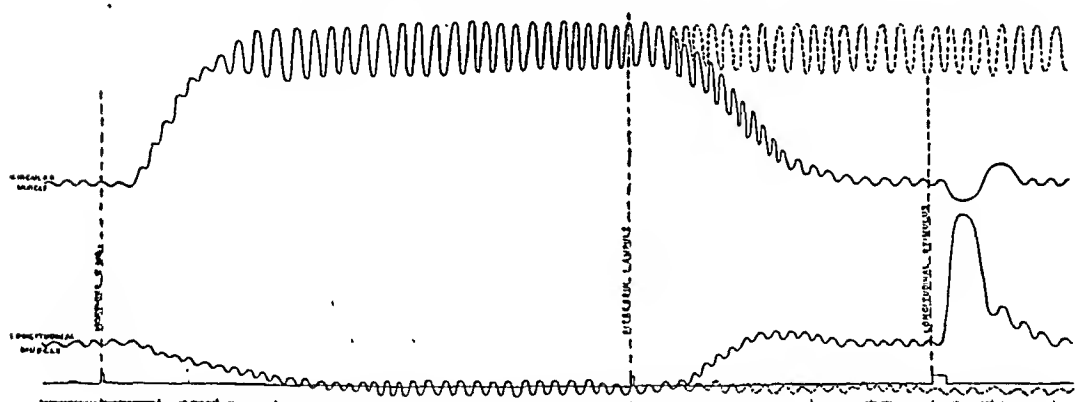


Fig. 11.—Diagrammatic reproduction of the effects of morphine and pitressin on the colon. About two minutes after the injection of morphine the circular muscle begins to contract strongly, with exaggerated excursions of the minor rhythmic contractions, while the oscillatory frequency of the colon is maintained for an hour or more (dotted line) unless pitressin is injected, in which case the bowel is released from the morphine spasm.

tained for thirty minutes or more. Pentobarbital sodium injected intraperitoneally for the production of general anesthesia in no way altered the reaction of the musculature to mechanical stimuli, nor was the tonus in general altered.

It is to be emphasized that the results of the aforementioned experiments on the action of drugs cannot as yet be accepted without reservation, as many are still under way and have not been sufficiently corroborated. The results stated, however, comprise a preliminary report, which will no doubt lend insight into the vast possibilities of experimental work made available by the exteriorized bowel graft.

## MISCELLANEOUS STIMULATION

*Heat and Cold.*—The effect of heat and cold were tested by placing on the mucosa pledgets of cotton on which hot or cold water was allowed to drip. Definite stimulation of the muscle was noted, but the effects were inconstant. In general, however, it may be stated that after the application of heat contraction of the longitudinal muscle predominates, while after the application of cold contraction of the circular muscle is stronger.

*Electrical Stimulation.*—Electrical stimulation by means of an inductorium invariably resulted in rapid and strong contraction of the circular muscle, without manifestations of activity in the longitudinal muscle.

## CONCLUSIONS

Further applications of the method are almost unlimited. By this means may be recorded the action of drugs applied locally or introduced systemically or by mouth. The effects of nerve stimulation, vasomotor reactions and local application of chemical or physiologic irritants may be demonstrated on the individual muscle coats. It is to be emphasized again that the bowel graft is pathologic, in that the continuity of the intestine has been interrupted and its mucosa exposed to an abnormal environment. Nevertheless, it is believed that the experiments described in this paper have been performed under conditions as nearly physiologic as are permitted by any other method in use at present and that the results have lent a new aspect to the understanding of the action of intestinal musculature.

# VARIATIONS OF THE CRANIAL VENOUS SINUSES IN THE REGION OF THE TORCULAR HEROPHILI

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## I. TYPES OF VARIATION

Le Double<sup>1</sup> has stated that to "describe one by one all the variations in the venous sinuses is impossible, and if it were done today, it would be incomplete tomorrow." Anatomically that may be true, but the variations of surgical interest, especially in the torcular region, may be definitely ascertained. It has long been recognized that the major volume of venous blood is directed through the right lateral sinus, whereas the straight sinus usually directs its major volume into the left lateral sinus. This right-sided predominance of the venous outflow from the brain was recognized at an early date by both Hunauld<sup>2</sup> and Morgagni.<sup>3</sup> For the sake of brevity, the evidence of right-sided predominance noted in studies of the skull, the jugular foramen and the dura has been summarized in table 1.

Just why the right lateral sinus should develop to carry the greater volume of blood in the majority of persons is still a moot point. Von Meyer,<sup>4</sup> Smith,<sup>5</sup> Bluntschli<sup>6</sup> and Zeiger<sup>7</sup> have sought in turn to explain this primary variation. From a perusal of their papers one is forced to the unsatisfactory assumption that it is a part of phylogenetic development. It is due perhaps to differences in channels of outflow and per-

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1. Le Double, A. F.: *Traité des variations des os du crâne de l'homme et de leur signification au point de vue de l'anthropologie zoologique*, Paris, Vigot frères, 1903.

2. Hunauld, P.: *Hist. acad. roy. d. sc. Paris*, 1730; cited by Le Double.<sup>1</sup>

3. Morgagni, J. B.: *Adversaria anatomica omnia*, Lugd. Bat., J. A. Langerak, 1741, vol. 6, p. 132, plate I, fig. 1.

4. von Meyer, H.: *Die Sinus transversus des Hinterhauptbeins*, Arch. f. Anat. u. Physiol. (Anat. Abt.) 1:271, 1877.

5. Smith, E. G.: On the Asymmetry of the Caudal Poles of the Cerebral Hemispheres and Its Influence on the Occipital Bone, *Anat. Anz.* 30:574, 1907.

6. Bluntschli, H.: Ueber die Asymmetrie der Sinus transversi durae matris bei Mensch und Affe, *Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte* 2:361, 1908.

7. Zeiger, K.: Ueber die Ursachen der Asymmetrie der Sinus transversi und sigmoidei beim Menschen, *Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres.* 19:184, 1922-1923.

haps to intracranial asymmetry that has been in turn influenced by asymmetrical growth of the extremity.

Five general types of variation of the sinuses are theoretically possible in the region of the torcular Herophili:

1. Common pool type. This is the classic and textbook picture of conformation of the sinuses and is actually encountered far less often

TABLE 1.—*Direction of Venous Outflow from the Brain as Noted in Studies by Various Authors*

Cases	Author	Date	Right	Left
<b>Skull</b>				
	Hunauld <sup>2</sup> .....	1730	+	0
14	Morgagni <sup>3</sup> .....	1741	+	0
100	Rüdinger, N.: Beiträge zur Anatomie des Gehörorgans, der venösen Blutbahnen der Schädelhöhle, sowie der überzähligen Finger: II. Ueber den Abfluss des Blutes aus der Schädelhöhle, Munich, Lit.-Artist Anstalt (T. Riedel), 1876.....	1876	71	27
512	Sperino, G.: Circolazione del capo. Rapporto fra la circolazione endo ed extracraniana, Torino, Camilla & Bertolero, 1884. ....	1884	269	78
100	von Spee, in von Bardeleben, K.: Handbuch der Anatomie des Menschen, Jena, Gustav Fischer, 1896, vol. 1. ....	1896	68%	13%
200	Le Double <sup>1</sup> .....	1903	137	29
400	Sturmshöfel, O. A.: Ueber die Eminentia cruciata des Hinterhauptbeines, Königsberg i Pr., O. Kummel, 1903.....	1903	232	61
	Zieger <sup>7</sup> .....	1923	60-70%	0
<b>Jugular Foramen</b>				
126	Thelle, F. W.: Ztschr. f. rat. Med. C: 227, 1855. ....	1855	46	24
100	Rüdinger .....	1876	71	27
449	Körner: Ztschr. f. Ohrenh. 19: 322, 1889. ....	1889	264	109
530	Budde, K.: Ueber Dehiscenzen in der unteren Wand der Paukenhöhle, Göttingen, W. F. Kaestner, 1891.....	1891	40-64%	26-30%
	Zuckerkandl, E., in Schwartz, H.: Handbuch der Ohrenheilkunde, Leipzig, F. C. W. Vogel, 1892.....	1892	54-60%	25-30%
<b>Dural Preparations</b>				
50	Dumont, J. N.: Les sinus postérieure de la dure-mère et le pressoir d'Herophile chez l'homme, Thèse de Nancy, no. 1, 1894. ....	1894	75%	
35	Henrici and Kikuchi <sup>8</sup> .....	1903	43%	
42	Mannu, A.: Internat. Monatschr. f. Anat. u. Physiol. 24: 304, 1907.....	1907	66%	
60	Vernicuwe <sup>13</sup> .....	1920	43%	
	Zeiger <sup>7</sup> .....	1923	66-68%	
35	Pfeiffer <sup>12</sup> .....	1930	60%	
50	Edwards <sup>10</sup> .....	1931	24	21
24	Gibbs, E. L., and Gibbs, F. A.: Anat. Rec. 59: 419, 1934. ....	1934	+	

than are the other patterns noted here. In this variation the longitudinal and the straight sinus meet in a more or less common pool from which the blood is directed to the lateral sinuses. The latter are ordinarily equal but may vary in size within narrow limits.

2. Plexiform type. This is the type of variation of the sinuses that should be expected from the bilateral embryologic development of this

region as detailed in the studies of Streeter.<sup>8</sup> Many subtypes are possible, but there is usually adequate intercommunication between the lateral sinuses. The longitudinal and the straight sinus may each be divided into two divisions, equal and unequal, and the lateral sinuses may be equal in size but usually are moderately dissimilar. The straight sinus may be divided into two branches, equal and unequal, with the longitudinal sinus single, the latter flowing usually to the right with the smaller half of the straight sinus, or this may be reversed. The longitudinal sinus may be divided into two equal or unequal branches with the straight sinus single, the latter usually flowing to the left side with the smaller branch of the longitudinal sinus. There is generally more pronounced difference in the size of the lateral sinuses in these last two subtypes.

3. Ipsilateral type. In this type the longitudinal sinus runs to one side, usually the right, and the straight sinus to the opposite side. Circulation between the lateral sinuses, if present, must take place through an additional direct channel or through the formation of a foramen, both types varying considerably in size. In the majority of cases the lateral sinus on the side of the longitudinal sinus flow will be much the larger.

4. Unilateral type. In this extremely rare conformation both the longitudinal and the straight sinus empty into one lateral sinus. The opposite sinus may be attenuated, being fed only by minute venous channels in the adjacent dura, or it may be completely absent.

In all the aforementioned general variations, the occipital sinus plays a minor rôle in the formation of the variation and in the task of conveying the outflowing volume of blood. It may be absent or extremely small.

5. Occipital type. The last main type of variation of the sinuses is directly concerned with the occipital sinus when it is of sufficient caliber to be of value in carrying blood. The commonest variation in the adult is the persistence of a large single or paired occipital sinus with large marginal sinuses, comparable to the pattern that is so common in the fetus or during the first few years of life. The second rare occipital abnormality is that in which either the longitudinal or the straight sinus or both in a common pool formation empty directly into a large occipital sinus at the expense of one lateral sinus, which will be found to be attenuated.

All these types, with the exception of 3 and 5, have been more or less aptly described by writers on this subject. Their findings are summarized in table 2.

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8. Streeter, G. L.: Development Alterations in the Vascular System of the Brain of the Human Embryo, *Contrib. Embryol.* 8:5, 1918.

## ANATOMIC STUDIES

The dural preparations were obtained from one hundred consecutive autopsies performed in the pathologic service of the Johns Hopkins Hospital. All specimens were excluded that had been involved in operative procedures. One was from a patient with thrombosis of the basilar sinus with the lateral sinuses secondarily involved and one from a patient with direct thrombosis of the lateral sinus. Five were from patients who had undergone cerebral trauma and seven from patients with cerebral

TABLE 2.—*Types of Variation of the Sinuses Noted by Various Authors*

Author	Date	Cases	Common Pool, Per- centage	Plexi- form, Per- centage	Ipsi- lateral, Per- centage	Uni- lateral	Occip- ital
Dumont, J. N.: Les sinus pos- térieure de la dure-mère et le pressoir d'Herophilus chez l'homme, Thèse de Nancy, no. 1, 1894	1894	50	8	80	12 ?	0	0
Henrici and Kikuchi <sup>9</sup> .....	1903	35	11	77	12 ?	0	0
Mannu, A.: Internat. Monat- schr. f. Anat. u. Physiol. 24 : 304, 1907	1907	42	4	68	28	0	0
Vernieuwe <sup>13</sup> .....	1920	60	42 ?	28	30 ?	1 case	1 case
Pfeiffer <sup>12</sup> .....	1930	50	26	60	5 ?	0	0
Edwards <sup>10</sup> .....	1931	50	12	48	36	4%	0
Lieutaud, J.: Essais anatomi- ques: Précis de la médecine pratique, Paris, Vincent, 1761	1761	..	..	..	..	1 case	
Hallett, C. H.: M. Times 17 : 50, 1848	1848	..	..	..	..	1 case	
Henle, J.: Handbuch der sys- tematischen Anatomie des Menschen, Braunschweig, F. Vieweg u. Sohn, 1871	1871	..	..	..	..	Noted	
Sperino, G.: Circolazione ve- nosa del capo. Rapporto fra la circolazione endo ed extra-craniana, Torino, Ca- milla & Bertolero, 1884	1884	..	..	..	..	..	1 case
Ballance: Lancet 1 : 1057, 1890	1890	..	..	..	..	1 case (skull)	
Sturmhöfel, O. A.: Ueber die Eminentia cruciata des Hin- terhauptblens, Königsberg i Pr., O. Kümmel, 1903.	1903	..	..	..	..	8 cases (skull)	18 cases (skull)
Le Double <sup>1</sup> .....	1903	..	..	..	..	3 cases (skull)	
Streit <sup>14</sup> .....	1903	..	..	..	..	..	1 case
Gleason: J. A. M. A. 98 : 379 (Jan. 30) 1932	1932	..	..	..	..	1 case	
Ersner and Myers: Laryngo- scope 43 : 800 (Oct.) 1933	1933	..	..	..	..	3 cases (x-ray)	

tumor with operative procedures not destroying the pattern of the sinuses. Fifty-seven of the patients were men, and forty-three, women; forty-nine, white persons, and fifty-one, Negroes. The age incidence by decades was fairly uniform, with a low figure of four in the 61 to 70 year period and a high of nineteen in the 31 to 40 year period. Twelve preparations were secured from infants less than 1 year old. All the material was studied in place in the skull on an average twelve hours after death.

The injection of gelatin or metal with formation of a permanent cast, perfusion estimation and simple dissection have been used by

previous investigators in the study of abnormalities of the sinuses. Since the surgical anatomy of the region of the torcular, with its complex architecture, was of particular interest, it was found by trial and error that careful dissection, with or without previous injection of a colored material, such as india ink, was most trustworthy. In the case of many specimens this technic was amplified and made permanent by sections stained with hematoxylin and eosin. An average of several diameters was used for the relative measurement of sinuses. The sinus pattern was dissected in place or removed in its entirety for section. During this procedure, the markings of the skull were defined in relation to the architecture of the sinuses. Roentgen studies were made of the typical patterns and the rare abnormalities after the injection of a mixture of gelatin, potassium chromate and lead acetate.

*Common Pool Type.*—Nine instances of this simple type of conformation of the sinus were observed in this series, a number that closely agrees with that given in previous reports. In all but two, the lateral sinuses were equal in size; in these two, the right lateral sinus was slightly larger. A very small occipital sinus entered the pool in three instances; a moderate-sized sinus entered the pool in one. In two a small occipital sinus entered the left lateral sinus within 1 cm. of the pool, and in three no occipital sinus was present. The markings of the skull were practically equal.

*Plexiform Type.*—There were fifty-six examples of this type of sinus pattern, and practically all the theoretical subtypes were observed. The pertinent details are summarized as follows:

Right lateral sinus greater than left lateral sinus.....	23
Slightly .....	15
Twice .....	7
Three times .....	1
Left lateral sinus greater than right lateral sinus.....	7
Slightly .....	3
Twice .....	4
Right lateral sinus equal to left lateral sinus.....	26
Longitudinal sinus or greater branch to right.....	25
Longitudinal sinus or greater branch to left.....	7
Longitudinal sinus divided equally.....	24
Straight sinus or greater half to right.....	8
Straight sinus or greater half to left.....	27
Straight sinus into torcular .....	3
Straight sinus divided equally .....	18
Intercommunication between lateral sinuses.....	56
Adequate .....	49
Slight .....	7
Intercommunication between lateral sinuses by combination of direct channel plus a branch of either main sinus.....	44
Intercommunication by branch of longitudinal sinus alone.....	8
Intercommunication by branch of straight sinus alone.....	4
Occipital sinus .....	
Small .....	45
Large .....	3
Absent .....	5
Abnormal .....	3
Markings of skull .....	
Apparently equal .....	23
Noticeable variation .....	18
Indefinite markings .....	13
None .....	2



The classic pattern of the plexiform type and the various subtypes are noted as follows:

Longitudinal sinus divided equally into two branches; straight sinus divided equally into two branches; right lateral sinus equal to left lateral sinus....	9
Longitudinal sinus divided equally into two branches; straight sinus divided equally into two branches; right lateral sinus greater than left lateral sinus	1
Longitudinal sinus divided equally into two branches; straight sinus divided, greater branch to the left; right lateral sinus equal to left lateral sinus.....	1
Longitudinal sinus divided equally into two branches; straight sinus undivided into left lateral sinus; right lateral sinus equal to left lateral sinus...	10
Longitudinal sinus divided equally into two branches; straight sinus undivided into left lateral sinus; right lateral sinus greater than left lateral sinus	1
Longitudinal sinus divided equally into two branches; straight sinus undivided into right lateral sinus; right lateral sinus equal to left lateral sinus	1
Longitudinal sinus divided equally into two branches; straight sinus into midtorcular region; right lateral sinus greater than left lateral sinus.....	1
Longitudinal sinus divided, greater branch to right lateral sinus; straight sinus undivided into left lateral sinus; right lateral sinus greater than left lateral sinus .....	9
Longitudinal sinus divided, greater branch to right lateral sinus; straight sinus undivided into left lateral sinus; right lateral sinus equal to left lateral sinus .....	3
Longitudinal sinus divided, greater branch to right lateral sinus; straight sinus undivided into right lateral sinus; right lateral sinus greater than left lateral sinus .....	4
Longitudinal sinus divided, greater branch to right lateral sinus; straight sinus undivided into midtorcular region; right lateral sinus greater than left lateral sinus.....	1
Longitudinal sinus divided, greater branch to right lateral sinus; straight sinus undivided into midtorcular region; right lateral sinus equal to left lateral sinus .....	1
Longitudinal sinus divided, greater branch to right lateral sinus; straight sinus divided equally into two branches; right lateral sinus greater than left lateral sinus .....	4
Longitudinal sinus divided, greater branch to left lateral sinus; straight sinus undivided to left lateral sinus; left lateral sinus greater than right lateral sinus .....	2
Longitudinal sinus divided, greater branch to left lateral sinus; straight sinus undivided to right lateral sinus; left lateral sinus equal to right lateral sinus .....	1
Longitudinal sinus divided, greater branch to left lateral sinus; straight sinus divided equally into two branches; left lateral sinus greater than right lateral sinus.....	3
Longitudinal sinus undivided to right lateral sinus; straight sinus divided, greater branch to right lateral sinus; right lateral sinus greater than left lateral sinus .....	1
Longitudinal sinus undivided to right lateral sinus; straight sinus divided, greater branch to left lateral sinus; right lateral sinus greater than left lateral sinus .....	1
Longitudinal sinus undivided to right lateral sinus; straight sinus divided equally into two branches; right lateral sinus greater than left lateral sinus	1
Longitudinal sinus undivided to left lateral sinus; straight sinus divided, greater branch to right lateral sinus; left lateral sinus greater than right lateral sinus .....	1

The plexiform type of sinus pattern illustrates well the tendency toward right-sided predominance, with the larger volume of the longitudinal sinus directed toward the right and the lesser volume of the straight sinus directed toward the left, or opposite, side. In only one instance was there a wide disproportion between the volumes of the lateral sinuses, and in only eleven were there noticeable differences as great as 2 to 1. There are uniformly full channels of cross-circulation at the torcular, through the divided sinuses or through a combination of

these and accessory channels. The place of the occipital sinus in this pattern needs little comment, and the obvious abnormalities will be discussed.

*Ipsilateral Type.*—This type of sinus pattern was noted in thirty-one preparations and was viewed with particular interest because of the character of its intersinus communication at the torcular. The longitudinal sinus entered the right lateral sinus undivided in twenty-six of these specimens and the left lateral sinus in the remainder. The straight sinus naturally followed the opposite course. The right lateral sinus was equal in volume to the left in fifteen cases, slightly larger in six, twice as large in five, three times as large in one and four times as large in one. The left lateral sinus was slightly larger than the right lateral sinus in two cases and twice as large in one. In 42 per cent of the cases, then, there was a right-sided overdevelopment, frequently of a major character.

The channels of intercommunication of the lateral sinuses at the torcular were of two types, and in no instance were both methods of cross-circulation seen in the same preparation. The first consisted of an oval foramen, sometimes slitlike, connecting the longitudinal and the straight sinus at the torcular as they veered in opposite directions to enter the lateral sinuses. In only one case was this foramen so minute as to be without value as a practical means of cross-circulation. Three foramina were small, measuring from 2 to 3 mm. in diameter, and four were large, measuring from 3 to 6 mm. in diameter.

The second type of cross-circulation seen at the torcular was that of an individual venous channel, uniformly short, the longest measuring 1.3 cm. in length. It usually connected the two sinuses at the right angles they made with the lateral sinuses. In ten preparations this single channel was large, measuring from 3 to 6 mm. in diameter (single in the majority of cases, in two preparations this channel was duplicated); in four it was small, measuring from 2 to 3 mm. in diameter; in seven it was minute, scarcely measurable, and in one all intersinus communication was absent (figs. 1, 2 and 3).

The occipital sinus was minute in ten cases, small in seventeen and absent in two. There appeared no definite tendency for this sinus to enter the longitudinal sinus, the straight sinus or the intersinus channel. There were two major abnormalities of the occipital sinus, which will be noted.

The markings of the skull were of equal intensity in fifteen cases, disproportionate in fourteen and indefinite in two.

The ipsilateral type of conformation of the sinuses shows an increasing percentage of right-sided predominating patterns, with the dispro-

portion increasing in extent as compared with the common pool and plexiform types. Lack of an adequate cross-circulation was noted in eight, or 25 per cent, of the preparations in this group. Henrici and

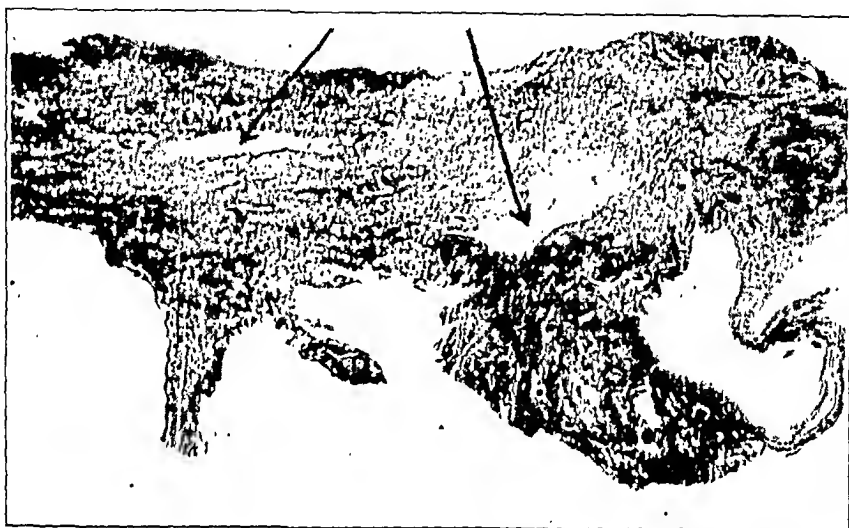


Fig. 1.—Photomicrograph (8 X) of a cross-section of the intercommunication between the lateral sinuses at the torcular in the ipsilateral sinus pattern. The arrows indicate the double channel. The large sinus is the occipital.

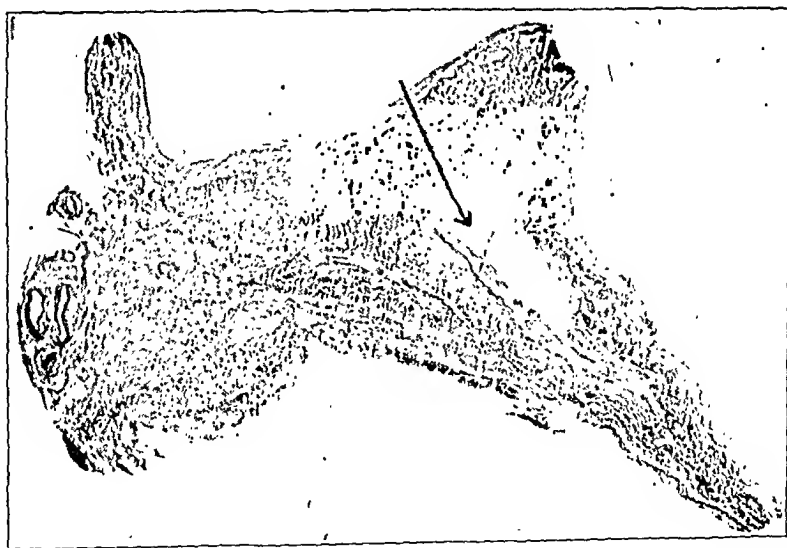


Fig. 2.—Photomicrograph (8 X) of a cross-section of the intercommunication between the lateral sinuses at the torcular in the ipsilateral sinus pattern. The arrow indicates the single channel.

Kikuchi<sup>9</sup> commented on three cases in which the intercommunication at the torcular was very small, one perhaps lacking, and mentioned eleven in which it was large, attributing little significance to the finding. In the eighteen cases in which Edwards<sup>10</sup> noted the ipsilateral type of conformation, he found "sometimes very little intercommunication." Klestadt<sup>11</sup> stated that lack of intercommunication between the lateral sinuses is a factor in some cases of cerebral back pressure in the course of thrombosis of a lateral sinus. Finally Pfeiffer<sup>12</sup> described one case found in the study of fifty preparations of the dura in which intersinus circulation was effected by a paired occipital sinus of small caliber. With these exceptions, scant attention has been paid to this important variation of the torcular.

*Unilateral.*—There were four examples of this rare conformation of the sinuses in the one hundred preparations of the dura studied. In three both the longitudinal and the straight sinus entered the left lateral sinus, with the absence of a true right lateral sinus; in one both major



Fig. 3.—Roentgenograms of an ipsilateral sinus pattern, showing: *A*, the "foramen" type of intercommunication at the torcular; *B*, minute direct channel intercommunication at the torcular, and *C*, the "direct channel" type of intercommunication at the torcular. *L* indicates the left lateral sinus; *R*, the right lateral sinus; *X*, the longitudinal sinus, and *S*, the straight sinus.

sinuses entered the right lateral sinus. In one of the unilateral patterns there was superimposed a gross occipital abnormality. The four examples are described in detail.

9. Henrici, C., and Kikuchi, J.: Die Varianten der okzipitalen Sinusverbindungen (Confluens sinuum) und ihr klinische Bedeutung, *Ztschr. f. Ohrenh.* **42**: 351, 1903.

10. Edwards, E. A.: Anatomic Variations of the Cranial Venous Sinuses: Their Relation to the Effect of Jugular Compression in Lumbar Manometric Tests, *Arch. Neurol. & Psychiat.* **26**:801 (Oct.) 1931.

11. Klestadt, W.: Zerebrale Symptomenkomplexe bei otogener Sinusphlebitis, *Ztschr. f. Laryng., Rhin. u. Otol.* **13**:83, 1924.

12. Pfeiffer, A.: Ueber die Variationen der Sinus der hinteren Schädelgrube besonders des Sinus occipitalis, *Ztschr. f. Hals-, Nasen- u. Ohrenh.* **25**:503, 1930.

1. The longitudinal sinus entered the left lateral sinus at the torcular undivided, and the straight sinus likewise emptied its entire volume into a quasi common pool formation at the same place. The left lateral sinus was huge, measuring 1.3 cm. at the sigmoid curve. At the torcular there was a minute channel, measuring from 1 to 2 mm. in diameter, which extended laterally, assuming the course and position of the absent right lateral sinus. At the jugular foramen, this sinus measured 4 mm. in diameter, being fed by three small veins in the dura of the right occipital and cerebellar fossae. The occipital sinus was minute and entered the left lateral sinus. There were no markings of the skull on the left side.

2. Both the longitudinal and the straight sinus emptied their entire volumes into the right lateral sinus by means of a quasi common pool formation at the torcular. From each sinus, 1 cm. from its entrance into the pool, a minute channel extended to the left side, the two uniting to assume the position and course of the absent left lateral sinus. At the jugular foramen, this attenuated sinus measured 3 mm. in diameter, being fed by two small veins in the dura of the occipital fossa. The right lateral sinus was huge, measuring 1.6 cm. in diameter. The occipital sinus was absent. There were no markings of the skull on the left side.

TABLE 3.—*Résumé of Abnormalities of the Sinuses*

Type	1. Predominance of the Lateral Sinus			2. Presence of Major Disproportion Between Lateral Sinuses			3. Presence of Inadequate Cross-Circulation at the Torcular		
	Cases	Right-Sided Pre-dominance	Left-Sided Pre-dominance	Equal	Cases	Right-Sided Pre-dominance	Left-Sided Pre-dominance	Small (2 to 3 Mm.)	Minute Absent
Common pool.....	9	2	0	7	9	0	0	0	0
Plexiform.....	56	23	7	26	56	8	4	7	0
Ipsilateral.....	31	13	3	15	31	7	1	7	8
Unilateral.....	4	1	3	0	4	1	3	0	0
		39%	13%	48%		16%	8%	14%	8%
								1%	

3. Both the longitudinal and the straight sinus entered the left lateral sinus, the latter at the torcular and the former at a point 2 cm. laterally. From the region of the torcular, two small channels extended to the right side to form an attenuated right lateral sinus, which measured 4 mm. at the jugular foramen, again being amplified by feeder veins from the occipital dura. The occipital sinus was absent. The markings of the skull on the right side were barely visible 2 cm. from the jugular foramen. The left lateral sinus measured 1.6 cm. at the sigmoid curve.

4. Both the longitudinal and the straight sinus entered the left lateral sinus, which measured 1.4 cm. in diameter. From the region of the torcular, a minute channel extended to the right side and assumed the course and position of the right lateral sinus. At the jugular foramen, this attenuated sinus measured 3 mm. in diameter, being fed by small veins in the occipital dura. A paired occipital sinus entered the left lateral sinus 0.5 cm. lateral to the entrance of the major sinuses. The right branch was relatively large, measuring 0.5 cm. in diameter, and without communicating with the left branch it entered the right marginal sinus and thus the right jugular foramen. The left branch of the occipital sinus was minute. There were no markings of the skull on the right side.

*Occipital Abnormalities.*—There were two general types of abnormality of the occipital sinuses, the first being a preservation of the fetal

pattern in the adult sinus system and the second an exaggeration of the occipital sinus and one marginal sinus, connecting either with the torcular or with either major sinus and aiding materially in the distribution of the volume of blood.

There were two instances of the first type, although less pronounced variations were frequent. Both occipital sinuses were single, dividing normally into the marginal sinuses and then emptying into the jugular foramina. Both, however, measured from 6 to 8 mm. in diameter, being as large in each preparation as the lateral sinuses.

There were four instances of the second general type. One has already been described in the discussion of the unilateral conformation of the sinuses, that is, a paired occipital sinus with one large branch extending from the left lateral sinus adjacent to the torcular to the right jugular foramen. In two cases an occipital sinus measuring from 6 to 8 mm. in diameter extended from the left lateral sinus to the left jugular foramen. Similar cases have been reported by Vernieuwe<sup>13</sup> and Streit,<sup>14</sup> in which in addition there was insufficient cross-circulation at the torcular. In the fourth case the straight sinus directed two-thirds of its volume to the occipital sinus and the remainder to a small lateral sinus. The longitudinal sinus emptied its entire volume into the left lateral sinus.

*Abnormalities of the Longitudinal and Lateral Sinuses (Local).—*There were two instances of abnormality of the longitudinal sinus adjacent to the torcular, both being evidence of failure to complete the bilateral embryologic anastomosis along the midline of the skull. In one the longitudinal sinus represented a double venous channel from the region of the posterior parietal lobe, about 7 cm. from the torcular. The second was a similar and shorter duplication of the sinus, starting 4 cm. from the torcular.

Two abnormalities of the body of the normal lateral sinus were observed, representing "local migration" changes of embryologic growth. They were noted as small outgrowths of the sinus wall, occurring at the sigmoid curve; abnormalities that have been termed "lateral sinus cloacae" by Ruttin.<sup>15</sup>

#### SUMMARY

The anatomic literature concerning abnormalities of the venous sinuses of the region of the torcular has been briefly reviewed.

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13. Vernieuwe: Les anomalies des sinus de la dura-mère: Leur signification clinique en otologie, *Rev. de laryng.* **42**:207, 1921.

14. Streit, H.: Ueber otologisch wichtige Anomalien der Hirnsinus, über accessorische Sinus und bedeutendere Venenverbindungen, *Arch. f. Ohrenh.* **58**: 161, 1903.

15. Ruttin, E.: Kloacken und Blindsackbildung am Sinus sigmoideus, *Acta oto-laryng.* **9**:217, 1926.

One hundred dural preparations of this region have been studied.

There is from this study anatomic evidence of: (a) right-sided predominance in 39 per cent of these specimens and left-sided predominance in 13 per cent, (b) major disproportion between the lateral sinuses in 24 per cent, (c) inadequate cross-circulation at the torcular in from 10 to 15 per cent, (d) a gross occipital abnormality in from 4 to 6 per cent, (e) absence of one lateral sinus in 4 per cent and (f) direct relationship between the volume of the sinuses and the markings of the skull.

The "normality" of the pattern of the sinus should be defined, it appears, not by its anatomic arrangement, because this may be variable, but by the efficiency of its response to dynamic studies and to pathologic changes within that pattern.

## II. VALIDITY OF THE QUECKENSTEDT TEST IN THE DIAGNOSIS OF THROMBOSIS OF THE LATERAL SINUS

Since the application of the Queckenstedt test to the diagnosis of thrombosis of the lateral sinus by Tobey and Ayer,<sup>16</sup> certain observations have been noted that are contradictory to those made in the original studies. These variations from the normal or expected reading fall into three groups.

The first comprises those cases in which a unilateral and false negative Queckenstedt reaction has been obtained in spite of the fact that thrombosis of the lateral sinus has been demonstrated clinically. Canuyt and Klotz<sup>17</sup> reported the case of a 20 year old farmer with a history of chronic otitis media on the right side for fifteen years. Ten days before admission there developed evidence of an acute infection involving the opposite ear, diagnosed as acute mastoiditis. A Queckenstedt test was performed to confirm the presence of thrombosis of the lateral sinus on the left side. In the lateral position, the spinal fluid pressure while the patient was resting was 48 cm. of water. Pressure on the right internal jugular vein caused an elevation in pressure to 80 cm. of water. With pressure on the left internal jugular vein, the manometer reading remained at 48 cm. A purulent thrombosis of the left lateral sinus was evacuated at operation. Twenty-three days after this procedure, a second Queckenstedt study was done. The pressure

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16. Tobey, G. L., Jr., and Ayer, J. B.: *Dynamic Studies on the Cerebrospinal Fluid in the Differential Diagnosis of Lateral Sinus Thrombosis*, Arch. Otolaryng. 2:50 (July) 1925.

17. Canuyt, G., and Klotz, A.: *Quelques considérations sur le signe de Queckenstedt à propos d'un cas de thrombophlébite du sinus latéral opéré et guéri*, Rev. d'oto-neuro-opht. 7:513, 1929.

during rest was 45 cm. of water. Compression of the right internal jugular vein induced a rise to 75 cm.; pressure on the left internal jugular vein caused a rise to 55 cm. of water. Thirty-five days after operation a third Queckenstedt test disclosed a resting pressure of 38 cm. of water. Compression of the jugular vein at this time gave practically equal responses, a rise on the right side to 52 cm. of water, and on the left, or thrombosed side, to 56 cm. Gaillard and Mayoux<sup>18</sup> reported a similar case. The preoperative spinal fluid pressure was 60 cm. of water. Pressure on the internal jugular vein of the affected side produced no response; pressure on the opposite side caused a rise of 17 cm. Later, an abscess of the lateral sinus was evacuated. Similar studies of dynamic changes fifteen days later revealed an elevation in pressure of 7 cm. in water on each side in spite of operative obliteration of the sinus. These observers expressed the belief that contradictory results were obtained because of dilatation of anastomosing venous channels, naming particularly the inferior petrosal sinus, the thyrolingual-facial trunk, the ophthalmic vein and the pterygoid plexus. Recanalization of the sinus appeared improbable in view of the relatively short time involved.

Mayoux<sup>19</sup> observed a third case that confirms this hypothesis. Prior to operation on a thrombosed lateral sinus, elevation of pressure of the spinal fluid on the compression of each jugular vein was of equal magnitude—40 cm. of water. After clinical evidence of extension of this thrombosis to the cavernous sinus, the Queckenstedt test on the thrombosed side caused the pressure to fall to 22 cm., whereas it remained at 40 cm. on the opposite side, indicating a suppression of collateral channels. The further observation of Whitehead<sup>20</sup> illustrates the mechanism of this collateral circulation. A rapid thrombosis of the lateral sinus on one side involved the torcular region. Papilledema developed, but after a tremendous dilatation of the facial, temporal and external jugular veins, the intracranial pressure subsided. Frenckner,<sup>21</sup> Stauffer,<sup>22</sup> Lemaître and Aubin<sup>23</sup> and Kopetzky<sup>24</sup> have reported identical cases.

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18. Gaillard, R., and Mayoux, R.: Sur l'épreuve de Queckenstedt dans les thromboses sinuso-jugulaires, *Rev. de laryng.* **48**:700, 1927.

19. Mayoux, R.: L'épreuve de Queckenstedt en otologie: Causes d'erreur; Interpretation des résultants, *Rev. prat. d. mal. d. pays chauds* **8**:563, 1928.

20. Whitehead, A. L.: A Case of Thrombosis of the Right Lateral Sinus in Which the Clot Extended Beyond the Torcular Herophili, *Proc. Roy. Soc. Med. (Clin. Sect.)* **2**:60, 1908.

21. Frenckner, P.: Some Experiments with Venosinography: A Contribution to the Diagnosis of Otogenous Sinus Thrombosis, *Acta oto-laryng.* **20**:477, 1934.

22. Stauffer, N. P.: Difficulties in Diagnosing Lateral Sinus Thrombosis, *Ann. Otol., Rhin. & Laryng.* **37**:890, 1928.



Further study with the Queckenstedt test both of patients with acute thrombosis of a lateral sinus and of patients at various intervals after exenteration of the lateral sinus is necessary to evaluate the course of this phenomenon. It is probable, however, that a unilateral falsely negative Queckenstedt response in the course of proved thrombosis of the lateral sinus has for its cause the appearance of a collateral circulation in adjacent cranial sinuses.

The second group embraces those rare cases in which a bilateral positive response to the Queckenstedt test is obtained, although pressure on both internal jugular veins simultaneously produces an adequate response. It is obvious that the amplitude of the rise on unilateral compression of an internal jugular vein is in proportion to the degree of resting pressure. Claude, Lamache and Aubry<sup>25</sup> studied fifty-eight Queckenstedt readings in thirty-four cases. In two normal persons there was no response to pressure on either jugular vein, i.e., a bilateral positive response to the Queckenstedt test, with the resting spinal fluid pressure at a low level. They attributed this false reaction to the inert vegetative nervous systems of these particular persons. Dandy,<sup>26</sup> in the article in which he first described the cerebral Queckenstedt test, described two cases of pertinent interest. In the third patient of his series, a young girl with symptoms of increased intracranial pressure, papilledema and no localizing signs, cerebral and spinal, dynamic studies gave a resting pressure of 140 mm. of water. On compression of either the right or the left internal jugular vein alone, there was no rise in pressure. Simultaneous compression gave a rise to 300 mm. of water. Ventriculography gave negative results. The pattern of the sinuses could not be studied. In the fourth patient, one with a rapidly progressing glioma of the brain stem, exactly similar findings were repeatedly registered. At autopsy, an occipital sinus, larger than either lateral sinus, was found to extend from the torcular to the jugular bulb on the left side. In the studies of variation of the sinuses in the region of the torcular described earlier in this paper, 4 per cent of one hundred dural preparations were found to exhibit a variation similar to that noted by Dandy. In all, there were extensive channels of cross-circu-

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23. Lemaitre, F., and Aubin, A.: Le signe de Queckenstedt dans un cas de thrombophlébite compliquée de méningite séreuse, *Arch. internat. de laryng.* **33**: 974, 1927.

24. Kopetzky, S. J.: An Observation on the Diagnosis of Lateral Sinus Thrombosis Contradictory to the Results of Tobey and Ayer, *Arch. Otolaryng.* **7**:532 (May) 1928.

25. Claude, H.; Lemache, H., and Aubry, M.: Compression des veines du cou et tension céphalorachidienne, *Compt. rend. Soc. de biol.* **96**:261, 1927.

26. Dandy, W. E.: Cerebral (Ventricular) Hydrodynamic Test for Thrombosis of the Lateral Sinus, *Arch. Otolaryng.* **19**:297 (March) 1934.

lation from one lateral sinus to the other, formed by the abnormal occipital sinus. It is probable that the unusual results of dynamic studies reported are due to such a venous pattern.

The third group comprises those instances in which a unilateral positive response to the Queckenstedt test is obtained, although the lateral sinus is not thrombosed and no abnormality of the sinus can be demonstrated. In the first of two cases reported by Gaillard and Mayoux,<sup>18</sup> exploration of the lateral sinus after a positive reaction to the Queckenstedt test revealed a perisinuous abscess obliterating the lumen of the sinus. Pressure on the internal jugular vein on the side of the supposed thrombosis had given an elevation of 2 cm. of water from the resting pressure, and the opposite side, a reading of 23 cm. Gardner<sup>27</sup> reported three cases of tumor of the cerebellopontile angle and one of glioma of the cerebellar lobe in which a positive or highly suggestive response to the Queckenstedt test was found prior to operation. Exploration in each instance disclosed complete or partial obliteration of one transverse sinus by the tumor.

Edwards<sup>28</sup> has pointed out the influence of abnormalities of the cranial venous sinus on the interpretation of readings of spinal fluid pressure. In a review of one hundred and fifty consecutive cases at the Boston City Hospital, he noted that one third of the readings showed differences that were clinically apparent. In one case, no rise occurred on one side, i.e., a positive response to the Queckenstedt test, although no abnormality could be demonstrated clinically. In a second case, pressure on the right internal jugular vein gave a rapid rise to 220 mm. of water and on release of pressure, a prompt fall to 110 mm., the resting pressure. Pressure on the opposite side gave a slow rise to a maximum of 190 mm. and an equally slow fall to the original reading. Paraffin casts of the lateral sinuses made at autopsy disclosed a smaller sinus lumen on the left side. Recent anatomic studies described earlier in this paper have verified the presence of a major disproportion in the size of the lateral sinuses in 24 per cent of one hundred dural preparations and an absence or extreme attenuation of one lateral sinus in 4 per cent of these cases. The following case is the first to be reported which illustrates both the clinical and the pathologic aspect of a completely false positive Queckenstedt reading obtained on the basis of an anatomic abnormality.

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27. Gardner, W. J.: The Tobey-Queckenstedt Test in the Localization of Tumors of the Cerebellopontile Angle, *Arch. Neurol. & Psychiat.* **20**:585 (Sept.) 1928.

28. Edwards, E. A.: Anatomic Variations of the Cranial Venous Sinuses: Their Relation to the Effect of Jugular Compression in Lumbar Manometric Tests, *Arch. Neurol. & Psychiat.* **26**:801 (Oct.) 1931.

## REPORT OF A CASE

E. R., a white policeman aged 34, was admitted to the accident room of the Johns Hopkins Hospital on March 30, 1934, in a semicomatose, delirious condition. The history was elicited from relatives. The family history was negative. The past history was irrelevant with the following exceptions: He had diphtheria as an infant and scarlet fever at the age of 12 years, followed by a chronic, intermittent discharge from the left ear, without tinnitus or noticeable loss of hearing. He was right-handed. The discharge from this low grade otitis media was sometimes clear and scanty and at other times purulent. There was no history of fever or headache. His present illness developed in the latter part of December 1933, with acute coryza, accompanied by an exacerbation of the aural discharge. He noted intermittent dull generalized headache and easy fatigability. Six weeks before admission, the pain in the head became localized in the left frontal and temporal regions and became severe, throbbing and constant. Five weeks before admission, a sharp pain developed in the left mastoid region, with a blood-tinged, foul-smelling aural discharge. Lavage of the canal of the external ear with a solution of sodium chloride gave no relief. Extraction of a tooth did not relieve the pain. Twelve hours before admission he became nauseated and vomited. His headache became more severe. Six hours before admission he lapsed into a semicomatose state.

*Examination.*—The temperature was 103 F., the pulse rate 130, the respiratory rate 30 and the blood pressure 140 systolic, 90 diastolic. The patient was well developed and adequately nourished. He was restless, necessitating restraint. He responded poorly to stimuli. The skin was hot and moist; no petechiae were noted. No local or generalized adenopathy was present. The skeleton was normal. The head was essentially normal except for definite tenderness over the left mastoid region, without cutaneous change. There was perforation of the left ear drum, with a purulent discharge. Examination of the fundi disclosed full veins without papilledema. Visual acuity and the visual fields could not be determined. Neurologic examination revealed little except the presence of a slightly stiff neck. The impression was that the condition was acute pyogenic meningitis secondary to mastoiditis and extradural abscess, on the left. The patient was admitted to the neurosurgical service.

Spinal puncture revealed increased pressure. A Queckenstedt test was not made. The fluid was cloudy, with 12,000 cells, practically all polymorphonuclear. The reaction to the Pandy test was one plus. No organisms were seen in a smear. Culture was later reported as negative.

The condition remained the same. No localizing signs of cerebral abscess were noted. Twelve hours after admission operation was performed—simple mastoidectomy and drainage of an extradural abscess on the left side. A culture was reported later as showing a heavy and pure growth of *Bacillus proteus*.

*Preoperative Queckenstedt Test.*—In the lateral position, a resting pressure of 200 mm. of water was noted. With pressure on the right internal jugular vein, a rise of pressure to 300 mm. of water occurred. With pressure on the left internal jugular vein, slight if any elevation was noted. Pressure on both internal jugular veins simultaneously caused a pressure of 360 mm. of water. The fluid was turbid, with 18,000 cells, all polymorphonuclear. No organisms were present in a smear. Culture was later reported as negative.

*Postoperative Course.*—High unremitting fever persisted, with profuse drainage from the mastoidectomy incision. The patient remained restless and delirious. The pulse rate gradually fell, the patient assuming a state of relative bradycardia.

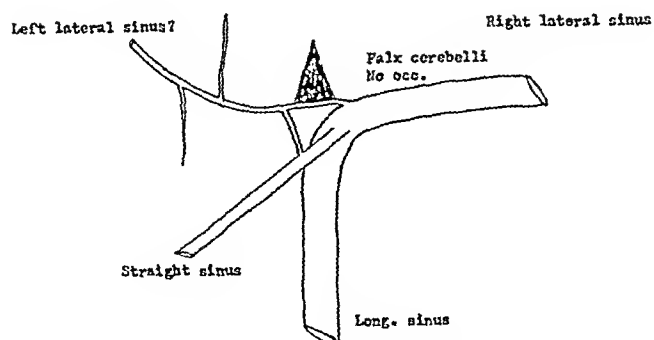


Fig. 4.—Diagram of the unilateral sinus pattern. No occipital sinus was present.

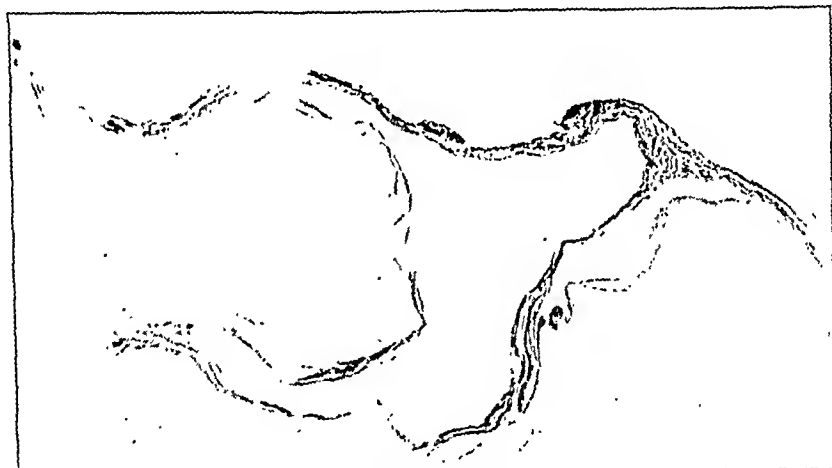


Fig. 5.—Cross-section (8 X) of the right lateral sinus at the sigmoid curve.

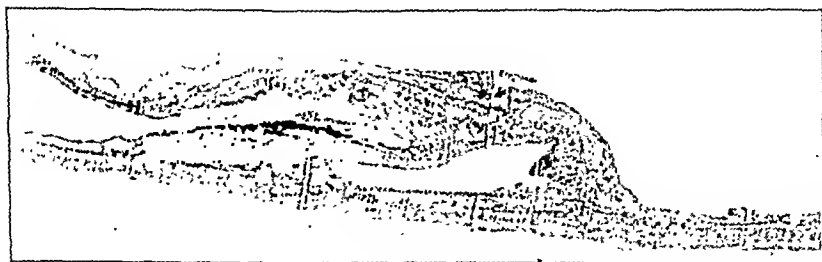


Fig. 6.—Cross-section (8 X) of the attenuated, or "substitute," left lateral sinus at the sigmoid curve.

On the fourth postoperative day definite right hemiplegia became evident. Death occurred while he was being prepared for operation.

*Autopsy Report.*—Acute mastoiditis had occurred, and operation had been performed. Perforation of the dura, was present, with acute meningitis. An abscess was present in the left temporal lobe of the brain. Lobular pneumonia was noted. Chronic urethritis was present. Dissection of the cranial venous system showed both the longitudinal and the straight sinus emptying into the right lateral sinus in a quasi common pool formation at the torcular. From each sinus, at a point 1 cm. from its entrance into the pool, a minute channel extended to the left side. An attenuated sinus, thus formed, represented in position and course the left lateral sinus, which was absent. It measured 3 mm. in its longest diameter at the jugular foramen. The right lateral sinus was huge, measuring 1.6 cm. in diameter. There was no occipital sinus. Markings of the skull were absent on the left side, whereas the course of the right lateral sinus was marked by the usual bony groove in the occipital bone (figs. 4, 5, and 6).

#### SUMMARY

The clinical course, studies of the dynamics of the spinal fluid and the pathologic changes in a case in which a completely positive but false unilateral Queckenstedt reaction was exhibited are recorded. This type of irregularity of the Queckenstedt reaction, when applied to the diagnosis of thrombosis of the lateral sinus, may be due either to external pressure on the sinus walls or to a major abnormality of the sinuses, as illustrated in this case. Such an anatomic abnormality has been reported present in 4 per cent of cranial sinus patterns.

Two other types of irregularity of Queckenstedt reaction, the unilateral false negative and the bilateral false positive, are discussed. They may have their common origin in channels of collateral circulation, either preexistent in the latter type or brought into play in the presence of a thrombosis in the former.

## A REVIEW OF UROLOGIC SURGERY

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### KIDNEY

*Anomalies.*—Campbell<sup>1</sup> said that, in the main, anomalies of the upper part of the urinary tract are significant because (1) the renal reserve is diminished, (2) the kidney is misplaced or malformed, (3) there is urinary obstruction, or (4) there is abnormal discharge of urine. In 193 of 282 infants and children with hydronephrosis whom he observed in series the condition was secondary to an anomaly of the upper part of the urinary tract (a frequency of 68.8 per cent). In 179 of 580 young persons with persistent pyuria whom he observed in series 206 anomalies of the upper part of the urinary tract were demonstrated (a frequency of 30 per cent).

The surgical importance of agenesis, aplasia or fused formation of solitary kidney is that the only functioning parenchyma may be unwittingly excised. Congenital ectopic kidneys, as distinguished from abnormally mobile organs, are firmly held in position by an anomalous vascular supply which makes it impossible to elevate them. Reduplication of a kidney permits resection when only half of the reduplicated organ is diseased. Half a kidney, usually capable of supporting life by itself, is preserved. Polycystic kidney in a child is seldom recognized during life, and unless infection, hematuria, stone or obstruction demands

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1. Campbell, M. F.: Surgical Treatment of Anomalies of Upper Urinary Tract in Children, J. A. M. A. 106:193 (Jan. 18) 1936.

intervention, the patient is best let alone; meanwhile, he should be treated as though he had nephritis. If profuse hematuria cannot be checked by blood transfusion or by intrapelvic injection of a 5 per cent solution of silver nitrate, or if there is extreme renal pain, nephrectomy or puncture of the large cysts must be considered. The mortality from nephrectomy is approximately 50 per cent, and that from nephrotomy 30 per cent, within the first postoperative month. In general, the patient lives longer if surgical treatment is not employed. If a large solitary renal cyst is present, the kidney should be resected unless the entire organ is destroyed. For advanced unilateral disease in horseshoe kidney heminephrectomy by division of the organ through the isthmus is the treatment.

Occasionally, the insertion of the ureter into the renal pelvis is unusually high, giving rise to the formation of a spur valve at the ureteropelvic junction. Unless mobilization of the ureteropelvic junction and high suspension of the kidney afford normal drainage, the ureter should be reinserted low in the pelvis to permit dependent drainage. Excision of the spur valve is not satisfactory. Nephrectomy is frequently necessary. An ectopic opening of the ureter requires surgical treatment only if the renal segment drained by the ectopic orifice is diseased or if the anomaly produces incontinence. Although a single ureter may have an ectopic orifice, it is usually the ureter from the upper pole of a reduplicated kidney that has the abnormal opening. In most instances this portion of the organ is diseased. When the ureter involved is single and the kidney is worth saving, transplantation of the ureter into the bladder is indicated. When the ureter with the ectopic opening is from a reduplicated kidney, ureteroheminephrectomy is usually indicated. A ureter with a blind ending is significant if the ureter and pelvis are converted into a cystic mass. The mass may simulate an abdominal tumor. Excision is the treatment; this may require nephrectomy or ureteroheminephrectomy. In the absence of superimposed infection, congenital stricture of the ureter seldom produces scarring. There is narrowing of the lumen of the ureter comparable to the congenital narrowing not infrequently seen in the intestinal tract, the bile duct and the urethra. Congenital stricture of the ureter is most common at the ureterovesical junction or the ureteropelvic junction and in the body of the ureter, respectively. Stricture of the ureter was demonstrated in 101 of 580 children with chronic pyuria. If mild, stricture at the ureterovesical junction may be dilated by bougies passed through a cystoscope. In infants, this dilation must usually be performed by the passage, side by side, of two, three or more no. 4 French catheters. Stricture of the body of the ureter will usually respond to cystoscopic dilation. Rarely the stricture is inflammatory

and surrounded by periureteral sclerosis; the liberation from this may enhance the results of instrumental dilation. Plastic operations on the body of the ureter for stricture can scarcely be expected to be successful. Stricture of the ureteropelvic junction in children commonly produces early hydronephrotic destruction of the kidney, which demands nephrectomy. Occasionally, the lesion is bilateral.

Congenital kinks of the ureter are rare. The kink is almost always found where the ureter leaves its peritoneal attachment to reach the kidney.

Only those aberrant vessels which compress the ureter are significant. If such vessels are present they will almost certainly run to the lower pole from the renal artery or vein, from the aorta or vena cava or from the common iliac artery or vein.

O'Connor<sup>2</sup> said that the more universal adoption of routine urologic examination has demonstrated that anomalies of the upper part of the urinary tract are not only common but often the underlying cause of obstruction and infection. In operation on a solitary kidney, it is important to minimize the operative trauma and to provide free urinary drainage; it is often advisable to decapsulate the kidney. The double ureter, either complete or incomplete, is the most frequent anomaly seen clinically. O'Connor's records show 32 incomplete and 9 complete duplications of the ureter. Two of the complete duplications were bilateral, with four ureteral orifices in the bladder. It has been his experience that the pathologic changes have been situated in the lower segment of the kidney in about 90 per cent of the cases. The upper half of the solitary kidney does not seem to be subjected to obstructive lesions as often as the lower half. Heminephrectomy is an established surgical procedure if half of the solitary kidney possesses a good function. O'Connor has performed this operation in 9 cases, without complication. Complete excision of the ureter, if it is incompletely duplicated, must accompany heminephrectomy. If complete duplication of the ureter is present, the ureter may be treated as it is in ordinary nephrectomy.

*Tumors.*—Smith<sup>3</sup> reported a series of 40 cases of tumor of the upper part of the urinary tract. There were 16 of hypernephroma, 10 of adenocarcinoma, 7 of carcinoma, 2 of fibrosarcoma, 1 of leiomyosarcoma, 3 of papillary epithelial carcinoma and 2 of tumor in which there was no report, either because the tissue was too necrotic or because the tumor was not removed.

2. O'Connor, V. J., in discussion on papers by R. Gutierrez, A. B. Hawthorne, M. F. Campbell and G. J. Thomas and J. C. Barton, J. A. M. A. **106**:199 (Jan. 18) 1936.

3. Smith, G. G.: Neoplasms of the Kidney and Ureter: A Report of Forty Cases, Am. J. Surg. **30**:130 (Oct.) 1935.



The epithelial tumor of the renal pelvis and ureter resembles that of the bladder. It may occur as papilloma, which is apparently benign but which may recur in malignant form. The incidence of epithelial tumor of the renal pelvis as compared with carcinoma of the kidney itself is said to be 1 to 11. The epithelial tumor metastasizes freely; the liver, lungs and bones are frequently affected. The papillary type often metastasizes along the ureter and into the bladder.

The relation of trauma to renal tumor has not been definitely established. The majority of patients give no history of trauma, but occasional cases are reported in which one may suspect a relationship. One case of this type was found in this series; three months before the initial mass and hematuria were noticed, the patient was injured by the caving in of a ditch. Several ribs on the side on which the tumor developed were broken.

The symptoms of renal tumor may be learned from a study of the 40 cases in this series. The first symptom in 26 cases was hematuria, in 14 pain, in 5 loss of weight, in 3 a palpable mass, in 3 digestive disturbance, in 1 irritability of the bladder and in 1 chills and fever. The cause of pain is not always the same. Some patients have a constant dull ache, which may be attributable to hydronephrosis, to pulling on the renal pedicle or to involvement of nerves by the growth. Sharp colicky pain is probably caused by the passage of clots through the ureter. It is usually referred to the renal region on the affected side, but it may be felt in the hypogastrium or even in the thigh. At the time of entering the hospital, 33 patients in the series (82.5 per cent) had a palpable mass in the renal region. The rate of growth of renal tumors unquestionably varies widely, but there is evidence that it may be slow. In this series there were 2 patients who were seen by Smith four and nine years, respectively, before they finally came to operation.

The operability of renal tumors is frequently an open question. In the first place, the existence of metastasis should be determined so far as may be possible. Roentgenograms should be made of the skull, long bones, thorax, lumbar vertebrae and pelvis. If a large tumor of the kidney is covered with a network of veins the size of lead pencils, hemorrhage is more satisfactorily controlled by the transperitoneal approach than it is by the lumbar approach. The lumbar incision should be used for the removal of a small tumor and when the diagnosis is uncertain. The initial incision for transperitoneal nephrectomy consists of an anterior median incision from the xiphoid process to the umbilicus. The peritoneal cavity should be explored, and the kidney should be palpated; if nephrectomy is decided on, a transverse incision, extending from the umbilicus at right angles to the first incision, is carried outward on the affected side as far as the tip of the twelfth rib. Exposure of the

kidney is aided by a sandbag or pillow placed beneath the lower thoracic and upper lumbar vertebrae.

In 3 of the 40 patients in this series, the kidney was explored but was not removed. Nephrectomy was performed in 32 patients, in 21 by the transperitoneal route and in 11 by the lumbar approach. Resection of the twelfth rib proved an aid in several patients in whom nephrectomy was performed by the lumbar approach. There were 7 operative deaths in the entire series, a mortality of 17.5 per cent. Two patients died within a few days of shock, and another patient died of bronchopneumonia. Three patients from whom kidneys were not removed died in less than four months after operation. Of the 30 remaining patients, 4 who had intra-ureteral growths died of recurrence; 2 died of disease of the heart one and two years, respectively, after operation, and 4 died apparently of recurrence. The latter patients lived from one month to eight years after operation. The average length of life was less than two years. Of the 10 patients who are living and apparently well, 2 have survived for one year, 2 for a year and a half, 1 for two years, 1 for three years, 1 for five years, 1 for eight and a half years, and 2 for ten years, a survival of 25 per cent. On the basis of this limited series, hypernephroma offers the best prognosis of any of the malignant tumors of the kidney.

Nichols<sup>4</sup> presented 4 cases which demonstrate the difficulties of making a correct diagnosis of epidermoid carcinoma of the pelvis of the kidney. The average age of the patients was 48 years. Two of the patients were women. Two were men. Hematuria was present in all. Renal calculus was present in 2 patients, and pyonephrosis was noted in the other 2. Palpable masses were present in 2. Three of the patients gave histories of pain, and 1 had had a previous injury. There were no clinical findings which in any way might be considered to be characteristic of epidermoid carcinoma. Roentgenologic examination was made in all the cases. In the first case a definite diagnosis of tumor of the kidney was made from the appearance of the organ in the stereoscopic roentgenogram of the urinary tract. This was the only definite evidence of tumor, and it demonstrated that the palpable mass was connected with the kidney. In the second case the presence of a growth of the kidney was also determined by pyelography, which revealed a tumor of the pelvis of the kidney and invasion of the renal cortex. This was interpreted as carcinoma of the kidney. In the third case the roentgenologic examination was of no aid in determining the presence of carcinoma of the kidney because of the large calculi in the affected kidney. A diagnosis of calculus pyonephrosis was made. In the fourth

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4. Nichols, B. H.: Squamous-Cell Carcinoma of the Kidney, *Radiology* 25:152 (Aug.) 1935.

case pyelographic findings indicated that tuberculosis of the pelvis of the kidney was present; however, eleven months later another pyelogram established the diagnosis of carcinoma of the kidney. In none of these cases was epidermoid carcinoma of the pelvis of the kidney suspected, and only after microscopic study of the tumor was this diagnosis made.

One case illustrates the presence of squamous cell carcinoma of the kidney in the presence of large calculi of the kidney associated with inflammation and leukoplakia. Such findings should suggest the possibility of the presence of this type of tumor at the time of examination. In this instance there was a history of an injury which might have been significant as an etiologic factor. The large multiple calculi may be considered as the logical contributing factor because of the irritation and the leukoplakia produced. Cure was not obtained in 3 of the cases reported, which indicates the necessity for early diagnosis. In the fourth case, in which examination of the specimen removed at operation revealed early squamous cell changes, the patient was alive two years after operation. Roentgenologic examination of the thorax should always be made when a tumor of the kidney is suspected. Metastasis to the thorax occurred in 50 per cent of these cases.

According to Silverstone,<sup>5</sup> pelvic new growths form from 5 to 7 per cent of all renal tumors; they may be divided into (1) benign papillomas, (2) papillary epitheliomas and (3) flat or alveolar carcinomas. The last group includes the squamous cell carcinoma, or epidermoid.

The squamous cell carcinoma of the renal pelvis is twice as common in males as it is in females. As elsewhere, it arises from epithelium that has undergone metaplasia as the result either of infection or of chronic irritation, usually from stone. There are two types. One type invades the renal parenchyma early and replaces the kidney. The other type obstructs the ureteropelvic junction so that there is hydronephrotic atrophy, without invasion of the parenchyma. Both types metastasize early and widely. There is no tendency toward implantation in the lower part of the urinary tract, as with papillary tumors.

Because the squamous cell growth is frequently associated with renal calculus, there is usually a history of long continued renal disease with increase in the severity of the symptoms marking the onset of neoplasia. Hematuria occurs in about 50 per cent of the patients. The diagnosis of squamous cell carcinoma of the renal pelvis carries with it a hopeless prognosis; the average duration of life is between ten and eleven months. Silverstone reported a case in which carcinoma was not associated with calculus or with infection.

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5. Silverstone, Maurice: Squamous Cell Carcinoma of the Renal Pelvis: Report of a Case, *Brit. J. Surg.* **23**:332 (Oct.) 1935.

*Calculus.*—Winsbury-White<sup>6</sup> said that in about 15 per cent of the cases renal lithiasis is bilateral. Such cases present a special problem because of the impairment of both kidneys and because the tendency to recurrence is greater.

It is not uncommon to find a disparity in the size of the calculi; there may be a large branched stone on one side and a small one on the opposite side. It is assumed that the smaller one is of more recent origin, and that lithiasis in one kidney predisposes to disease in the opposite one. This is supported by the facts that there is a greater incidence of bilateral lithiasis late in life, and that in unilateral disease removal of the calculus is very infrequently followed by the formation of one in the opposite kidney.

It is characteristic of large branched bilateral calculi that they do not cause pain until late in the disease. They produce little obstruction at the ureteropelvic junction because of fixation of the limbs in the calices, which prevents the stone from sinking into the outlet of the renal pelvis. When there is marked disparity in size, it is usually the smaller stone which causes pain and obstruction, calling attention to the disease.

Each case presents its own problem of treatment because of the variations in the size of renal stones, in the degree of renal function that remains and in the severity of the infection. Winsbury-White considered the treatment of the various conditions encountered in 36 cases which he observed. In general, he concluded that both kidneys should never be operated on at the same time. Operation on both kidneys carries a mortality of about 50 per cent. The better side should be operated on first, so that if, when operation is performed on the other side, there is some factor which indicates nephrectomy, one is better able to decide whether such a procedure is feasible.

In the presence of large branched bilateral stones, no intervention is advisable unless there is some complication, such as obstruction, pyonephrosis or perinephritic abscess. Under these circumstances, permanent nephrostomy not only relieves the acute condition but improves function, relieves infection and prevents recurrence.

When there is great disparity in the size of the stones, the side with the small stone should be operated on first because of the greater likelihood of obstruction and resulting anuria on that side.

According to Gray,<sup>7</sup> Leriche and Policard contended that in the presence of hypercalcemia deposition of calcium takes place in con-

6. Winsbury-White, H. P.: Bilateral Urinary Calculus, *Brit. J. Urol.* 7:235 (Sept.) 1935.

7. Gray, J.: The Effects of Obstruction of the Urinary Tract, with Particular Relation to the Formation of Stones, *Brit. J. Surg.* 23:451 (Oct.) 1935; The Effect of Experimental Interference with the Blood-Supply of the Kidneys, with Particular Reference to the Formation of Stones, *ibid.* 23:458 (Oct.) 1935.

nective tissue of low metabolism if the blood supply is diminished. To test this theory in relation to the formation of renal calculi, Gray conducted the following experiments: In 40 rabbits the blood supply to one kidney was reduced by ligating one of the two terminal branches of the renal artery. Twenty of these rabbits received a normal diet and the remaining twenty received a diet to which lime and concentrated extract of vitamin D were added in sufficient quantities to produce hypercalcemia. It was found that the latter diet markedly increased the amount of calcium in the urine and diminished the amount of phosphate relatively or absolutely.

Under these circumstances it was found that no stones were formed in the normal kidneys in either group, but that stones occurred in the damaged kidneys of 15 per cent of the rabbits which received the normal diet and of 45 per cent of those which received the diet to which calcium and vitamin D had been added. The stones were large and were always found in the pelvis or calices, never in the parenchyma. The urine was cultured each time that an animal was killed, and only in an occasional one was any infection shown to be present. There was nothing to suggest that this played any part in the pathologic changes.

Histologic studies of the kidney in which stones were formed revealed marked desquamation of the epithelium of the renal pelvis and frequently, if not always, deposition of calcium in relation to the damaged regions and around the desquamated epithelium.

Ten rabbits were fed oxamide in addition to their normal diet, after preliminary ligature of a vessel in one kidney. In 1 rabbit definite stones were formed in the normal kidney, while in 5 rabbits stones were formed in the kidney with the ligature.

The truth of the theory of Leriche and Policard is demonstrated by the results in this series of experiments. The two important factors in the production of a calculus seem to be (1) a dietetic factor, for instance, a calcium-phosphorus imbalance or an excess of some foreign substance such as oxamide, and (2) the local factor which leads to the precipitation of the substances which form the stone.

In view of the fact that the stones always formed in the pelves or calices, it seems that a cavity is necessary. There was always some abnormality of the epithelial lining, and frequently the stones could be demonstrated forming around desquamated epithelium. This suggests that an important factor in the formation of a stone is an alteration in the epithelium which might act by producing variations in surface tension or, more directly, by giving rise to desquamation, the dead epithelial cells then acting as a nucleus for the stone.

With another group of animals, Gray conducted the following experiments to determine the relation of obstruction in the urinary tract to the formation of stones: In 36 rabbits one ureter was ligated so as to produce complete obstruction, and in 4 rabbits one ureter was ligated so as to produce partial obstruction. Twenty-five of the rabbits received a normal diet, and the remaining ones, including those with partial obstruction, received a diet to which calcium and vitamin D had been added in order that hypercalcemia might be produced. Stones were not formed in any of the normal kidneys or in any of the kidneys in which there was complete obstruction. However, in the 4 rabbits which had partial ureteral obstruction and which received the diet containing additional calcium and vitamin D stones formed in the kidney on the obstructed side. It appears from this that there is no tendency toward the formation of stones (even in animals which receive a diet that predisposes to the formation of stones) when renal function is almost entirely absent.

Sisk and Bunts<sup>8</sup> reported 5 cases of nephrolithiasis in which the calculi developed after severe injury to, or disease of, the bone. In 1 case the stones were composed mainly of magnesium phosphate, and in 3 cases, chiefly of calcium phosphate with some calcium carbonate. There seemed to be a definite relationship between renal calculi made up of a phosphate (usually calcium phosphate) and skeletal decalcification. This is attributed to the excessive excretion of calcium salts and other salts that occurs from bones through the kidneys. Spontaneous dissolution and passage of these calculi occasionally occur. Diets with an acid base and acidifying drugs, such as ammonium chloride, increase the elimination of calcium through the kidneys, increase the acidity of the urine and may be beneficial in preventing the formation of calculi of this type.

*Tuberculosis.*—Addison<sup>9</sup> said that tuberculosis of the kidney, apart from the miliary type, is among the rarer manifestations of the disease of childhood, and comparatively few instances have been observed in children in the first decade of life. Miliary tuberculosis of the kidney is frequently disclosed at necropsies on children who died of tuberculous meningitis or of general tuberculosis. During a period of one year Addison saw tuberculosis of the kidney in 10 children; 7 had other active lesions, usually of the spine or hip. The youngest child was 4 years of age.

8. Sisk, I. R., and Bunts, R. C.: Spontaneous Dissolution of Renal Calculi, *Tr. Am. A. Genito-Urin. Surgeons* 28:149 (June) 1935.

9. Addison, O. L.: Tuberculosis of the Kidney in Childhood, *Brit. M. J.* 2:565 (Sept. 28) 1935.

In the earliest stages of invasion of the kidney by tubercle bacilli there are no symptoms; the only sign is slight pyuria, which is usually intermittent and discoverable only on microscopic examination. Hematuria is generally the first objective symptom; this usually is slight and frequently is present only for twelve or twenty-four hours. The hemorrhage recurs at intervals and is associated with increasing pyuria; in the later stages, when there is general involvement of the bladder, hematuria is usually a constant symptom. The urine is acid and, until the disease is well advanced, is seldom contaminated with other organisms.

Diagnosis depends on finding the tubercle bacilli in the urine. In the presence of unexplained chronic or intermittent pyuria a careful examination for this organism should be made. The bacillus is difficult to find in the early stage of infection, and it often is present only intermittently. In the early stage, before there are clinical symptoms, such as constant pyuria and increased frequency of micturition, the disease progresses slowly; it may last many months or even years before general involvement of the kidney occurs.

The child who shows the early stages of infection should be treated in a sanatorium, preferably, at first, in bed. One in whom the disease is advanced and unassociated with other active lesions, should be submitted to nephrectomy provided that no tubercle bacilli are found on catheterization of the ureter of the other kidney and that renal function is within normal limits. If the second kidney is infected and pyelography shows that the lesion is small and the function is satisfactory, nephrectomy may be advisable. The prognosis after the kidney has been removed is favorable. Of 5 of Addison's patients in whom nephrectomy was performed, 3 recovered rapidly and showed the urine free from tubercle bacilli in two or three months. The youngest patient was 9 years old. Two of the patients who survived had been in the advanced stage of the disease. One had had severe involvement of the bladder.

*Actinomyces*.—Kretschmer and Hibbs<sup>10</sup> said that actinomycosis of the kidney is rare in infants and children. A survey made by Sanford and Voelker of 670 cases of actinomycosis in the United States revealed only 45 in children. The kidney was one of the least frequent sites of the disease. Edwards, in his review of cases of juvenile actinomycosis, said that in 50 per cent it occurred in the region of the head or neck, in 20 per cent in the thoracic viscera, and in an equal number in the abdomen.

*Actinomyces bovis* is a facultative anaerobe which is rather easily cultured. On a solid medium it penetrates typically below the surface.

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10. Kretschmer, H. L., and Hibbs, W. G.: Actinomycosis of the Kidney in Infancy and Childhood, *Tr. Am. A. Genito-Urin. Surgeons* 28:93 (June) 1935.

It is readily killed by heat. The actinomycetes which are derived from vegetable sources are aerobic. *Actinomyces bovis* has been obtained only from animal sources and probably lives on the mucosa of the mouth and digestive tract. Edwards concluded that it is a normal inhabitant of the secretions of the mouth and gastro-intestinal tract of man and animals, but that in certain instances it may be carried into the tissues, where it is able to establish itself. When the fungus is present in the mouth and gastro-intestinal tract, its implantation into the tissues may be favored by trauma, disease and accompanying organisms. While the actinomycetes of vegetable origin are not identical with that which causes actinomycosis among human beings, trauma of the buccal mucosa may be a factor in producing disease from their presence.

In the treatment of unilateral renal actinomycosis, nephrectomy is the operation of choice unless there is also extensive involvement of other organs. As in renal tuberculosis, the absence of disease in the other kidney must be established by careful study of the urine and by pyelography. Various treatments have been suggested for the operative wound, such as leaving it open and packing it with iodoform gauze. Medical treatment after nephrectomy has been recommended, and the drugs that have been most widely used are potassium iodide and copper sulfate.

*Carbuncle*.—Graves and Parkins<sup>11</sup> described carbuncle of the kidney as a circumscribed multilocular abscess of the renal parenchyma involving varying amounts of the substance of the organ. It is probably metastatic in most instances, and usually arises from a primary focus of infection elsewhere in the body. The causative organism is most frequently *Staphylococcus aureus*. The clinical interest in this lesion relates to its relative rarity and to the difficulties in diagnosis.

An analysis of the 66 previously reported instances of renal carbuncle together with the case reported by Graves and Parkins revealed that the disease usually follows a primary staphylococcic infection of the skin. Forty-two of the patients had furuncles, carbuncles or other superficial abscesses. The respiratory tract was the apparent primary focus in only 4 of the patients; 2 patients gave histories of trauma in the region of a kidney, and 1 had had chronic pyelitis. Forty-one of the patients were males, and 25 were females; in 1 instance, the sex was not given. Three of the patients were infants. Two of the latter were 8 weeks of age. One was 9 months old. The time between the original superficial infection and the onset of the illness of the kidney varied from a few days to many months, the average being fifty-three

11. Graves, R. C., and Parkins, L. E.: Carbuncle of the Kidney, *Tr. Am. A. Genito-Urin. Surgeons* 28:41 (June) 1935.



days. The onset of the carbuncle of the kidney was marked by pain in the general region of the flank. This was the initial symptom in 46 of the cases. That the pain was not definitely placed or well localized was evidenced by the difficulty in diagnosis, as shown by the fact that there was an average delay of sixty-one days before proper treatment was instituted in 42 of the cases. Malaise, progressive prostration and fever, which often persisted for many weeks, were associated with the pain in most of the cases. Chills were frequently reported, and signs of pleuritic irritation were not uncommon. There was tenderness in or near the kidney in almost every case. Inflammatory changes extending through the diaphragm often resulted in misleading signs in the thorax, on the affected side. Incision and drainage were performed on 19 of the patients, with a mortality of 31.5 per cent; nephrectomy was performed on 39, with 7 deaths (17.9 per cent); the end-results in 2 patients were not given. Removal of the carbuncle from the kidney by enucleation was performed satisfactorily in 5 patients, all of whom recovered.

Roentgenographic and clinical evidences of fixation of the diaphragm on the affected side are of marked diagnostic significance. Often, particularly on the left side, if there is marked infection in or around the kidney, there is a direct extension of the inflammation through the diaphragm, which results in its limitation or fixation as well as in confusing signs and symptoms in the adjacent lung and pleura. When such evidences are present fluoroscopic as well as roentgen examination of the thorax should be made.

The treatment of renal carbuncle is surgical. The earlier and more accurate diagnosis of a suppurative process within the kidney may result in the more prompt use of surgical treatment. The choice of procedure will vary with the condition of the patient. There are three methods of treatment: (1) incision and drainage followed by nephrectomy if necessary, (2) primary nephrectomy and (3) enucleation of the carbuncle. The lowest mortality in this group of cases was obtained with the last-named procedure. The next lowest mortality (17.9 per cent) followed nephrectomy, and, in general, this should be the treatment of choice. Nephrectomy in two stages is valuable if the patient has become seriously depleted by the infection.

*Hydronephrosis.*—Wilder and Doolittle<sup>12</sup> reported a case of gigantic hydronephrosis in which the kidney contained more than 6 liters of fluid. The kidney was successfully removed. Papin used the term "gigantic" to describe hydronephrotic kidneys which fill a large portion of the abdomen. He referred to cases of hydronephrosis of long

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12. Wilder, W. O., and Doolittle, L. H.: "Gigantic" Hydronephrosis, *J. Urol.* 34:356 (Nov.) 1935.

standing in which the kidneys contained 30 liters and 36 liters of urine, respectively, and to the case reported by Glas, in which the kidney gave up 30 gallons (110 liters) of fluid at necropsy. Papin also mentioned the cases which recently have been reported by Baldwin, by Auscherlik and by Mosny, Javal and Dumont. In the case reported by Baldwin, the kidney of a child who was 1 year of age contained 2,500 cc. of fluid. Auscherlik found 5 liters of fluid in the kidney of a child aged 3, and Mosny, Javal and Dumont found 30 liters of urine in the kidney of a woman aged 25. Hahn reviewed the literature and reported 2 additional cases, that of a boy aged 8 who had 4 liters of fluid in the right kidney and that of a child whose right kidney contained about 2 liters of fluid. Papin said that the majority of patients in whom enormous hydronephrotic kidneys develop are children or young persons. Occasionally, such kidneys occur in older persons. J. Van D. Young recorded a case in which a woman 38 years of age was operated on for a cyst of the right ovary and was found to have hydronephrosis of the right kidney, from which more than 8 quarts (30 liters) of fluid was removed.

Howze<sup>13</sup> said that giant hydronephrosis is of infrequent occurrence. A review of the literature over a period of twenty-five years revealed only 32 cases. The size of the hydronephrotic kidney varied. In an infant the kidney contained 900 cc. of fluid, and in another patient 50 liters of urine was removed by abdominal paracentesis. Thirty of the patients were operated on; 1 patient died following repeated abdominal paracentesis, and the condition of another was diagnosed at necropsy. Nephrectomy was performed by the transperitoneal route in 11 patients.

Howze reported a case in which the diagnosis was made by cystoscopic study and pyelography. The significant features in this case were: (1) the enormous size of the renal pelvis; (2) the relatively few symptoms over a long period; (3) the fact that a hydronephrotic kidney of such caliber retained a third of the function of a normal kidney, as shown by the specific gravity of the urine and the amount of urea excreted by the affected kidney, and (4) the fact that a satisfactory pyelogram was obtained with a small quantity of opaque medium. Following the removal of 1,000 cc. of fluid from the affected kidney by ureteral catheterization, 50 cc. of skiodan was injected. A roentgenogram revealed an enormous hydronephrotic sac which extended from the diaphragm to the bony pelvis and which crossed the median line and overshadowed a large portion of the outline of the opposite kidney. The patient continued to have some discomfort, and, later, 2,300 cc. of fluid was removed. There was complete relief from

13. Howze, C. P.: Giant Hydronephrosis: Report of a Case, *Tr. Am. A. Genito-Urin. Surgeons* 28:1 (June) 1935.

abdominal symptoms until the time of the patient's sudden death from cerebral thrombosis, four weeks later.

*Pseudohydronephrosis.*—Crabtree<sup>14</sup> said that pararenal pseudohydronephrosis is a rare disease. If the condition is neglected, renal destruction and death may ensue. Its characteristic symptom is continued disability. Discomfort after improvement from renal injury may reasonably be expected to occur; this may be followed at some later date by exacerbation of symptoms, after which renal tumor appears. Hematuria may be absent; if present, it is usually of short duration. An increase in temperature is not to be expected, and fever is usually low or absent during the quiescent stage of the disease. It may be more marked during exacerbation of symptoms and rapid growth of the tumor. The leukocytic count is usually low. Even in the latent stage the disease is debilitating.

Three factors which are necessary for the production of the disease are (1) trauma or perforation which opens the calix, pelvis or ureter within the fatty capsule of the kidney, (2) maintenance of the opening beyond the normal healing period and (3) acquired or preexisting obstruction of the ureter. The disease is rapidly destructive to the kidney. Preservation of the kidney depends on early recognition of the condition and relief of the ureteral obstruction. Separated fragments of tissue of the kidney are usually not sufficiently viable to allow reparative procedures to be employed at some later time after the injury. Repair of the lesion is indicated if the condition has been present for a considerable time.

Treatment by drainage or paracentesis will not be satisfactory except in cases in which the renal damage has been sufficient to produce auto-nephrectomy. In most instances in which the condition has been present for a long time nephrectomy is necessary. This operation is not always possible because of the fibrous wall of the sac, which may enclose the major portion of the kidney and its pedicle. Demonstration of urine in the sac or of an opening into the renal pelvis is necessary to distinguish the disease from serous cysts.

*Trauma.*—Turton and Williamson<sup>15</sup> reported a case of rupture of a congenital solitary kidney and reviewed 4 similar instances collected from the literature. Their patient was a boy aged 12 years who had fallen off a gate and landed on his left flank. His chief complaints were pain in the left loin, vomiting and hematuria. The abdomen was rigid, and there was impaired resonance on the left side which increased

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14. Crabtree, E. G.: Pararenal Pseudo-Hydronephrosis with Report of Three Cases, *Tr. Am. A. Genito-Urin. Surgeons* 28:9 (June) 1935.

15. Turton, J. R. H., and Williamson, J. C. F. L.: Traumatic Rupture of the Congenital Solitary Kidney, *Brit. J. Surg.* 23:327 (Oct.) 1935.

to absolute dulness in the flank. His condition improved so that one week after the injury the urinary output was 1,200 cc., the urine was clear, and the area of impaired resonance had receded into the flank. However, on the eleventh day anuria and pain in the left lower abdominal quadrant were noted, and the patient's general condition became worse. An incision was made in the left flank, and a large amount of urine and some clots were evacuated from the extraperitoneal tissue below the left kidney. The patient died on the operating table.

Necropsy disclosed a rupture of the left kidney which extended from the lower pole to the pelvis. There was a congenital absence of the kidney, adrenal gland and ureter on the right side.

In each of the 4 other instances of traumatic rupture of a congenital solitary kidney reported in the literature the right kidney was absent, but the absence was not suspected and a left nephrectomy was performed.

The necessity for determining whether or not a second functioning kidney is present in every case of renal injury is obvious. The best method is excretory urography. When this is not possible and when operation is made urgent because of severe hemorrhage, palpation of the contralateral kidney through the opened peritoneum is imperative before nephrectomy is done. If the ruptured kidney is proved to be a solitary kidney, the operative measures are limited to conservative suturing or partial nephrectomy to arrest hemorrhage.

Colston and Baker<sup>16</sup> presented a series of 13 cases in which clinical examination or operation revealed definite pathologic changes either in the kidney or in the perirenal tissue. The patients had been injured severely in the region of the kidney at varying intervals of time before they appeared for examination. The relationship of the trauma to the conditions described was definitely established in each case; the lesions encountered in these cases varied from those causing minimal disability to those causing complete incapacity.

There must be complete familiarity with the changes that may occur in the kidney or perirenal tissue as late results of injuries to the kidney and the necessary steps taken to prevent their development. When injury to the kidney is suspected the patient should be subsequently studied with special reference to the demonstration of persistent perirenal extravasation. This should be readily recognized as a palpable mass or in the obliteration of the outline of the kidney and psoas shadow on roentgenologic examination. If hematuria has occurred as the result of an accident, an injury to the pelvis or to the calices should be suspected. Subsequent pyelographic studies should be carried out

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16. Colston, J. A. C., and Baker, W. W.: Late Effects of Various Types of Trauma to the Kidney, *Tr. Am. A. Genito-Urin. Surgeons* 28:171 (June) 1935.

to ascertain that distortion or obstruction has not occurred as a result of formation of scar tissue, since it may lead later to serious damage to the kidney. In the emergency which exists after any suspected injury to the kidney, the surgeon should keep in mind a clear perspective of the ultimate changes that may result.

*Extravasation from the Pelvis.*—Hortolomei, Ornstein-Streja and Burghel<sup>17</sup> made an intensive experimental study of cases of extravasation from the pelvis of the kidney, and advanced a number of hypotheses with reference to the pathogenesis in these cases. They pointed out that between the pressure of the secretion of the urine and that of its excretion caused by the tonicity and peristalsis of the pelvis there exists a hydrodynamic equilibrium which assures the proper functioning of the excretory apparatus. When this equilibrium is disturbed through increase of intrapelvic pressure, the fluid in the pelvis flows out of its cavity, a phenomenon which is known as extravasation from the pelvis. The fluid thus extravasated nearly always penetrates the kidney and easily enters the venous or the lymphatic circulation, resulting in a pyelovenous or a pyelolymphatic reflux. Extravasation into the tubules is relatively rare in sound kidneys, but overflow into the calices is common.

The pressure necessary to produce rupture into the calices varies from 20 to 80 mm. of mercury; in most cases rupture of the human kidney has occurred at a pressure of from 30 to 50 mm. If the amount of liquid extravasated is small, it remains localized in the sinus of the kidney between the lips of the hilus and forms a sinusal or primary extravasation. But if the reflux continues through the breach it may produce a retroperitoneal, a perivascular or a subcapsular extravasation, all of which can be identified in the respective pyelograms.

The authors indicated the rôle played by extravasation in the production of numerous morbid processes the pathogenesis of which has hitherto been little understood. The production of extravasation by artificial filling of the pelvis has given a great deal of information with reference to clinical extravasation, since it permits the graphic control of the production of reflux and fixes it on the roentgenogram, thus serving as a point of departure in the study of the clinical expression of each type of extravasation.

In a healthy pelvis the production of an extravasation in the course of pyelography produces practically no clinical manifestations except a painful sensation, which is the result of distention. After the production of an extravasation in an infected pelvis the appearance of hematuria following pyelography is often characteristic, and the reflux of the septic content of the pelvis into the renal parenchyma may cause

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17. Hortolomei, N.; Ornstein-Streja, M., and Burghel, T.: Les extravasations du bassinet, *J. d'urol.* 38:481 (Dec.) 1934.

alarming clinical symptoms, chief among which is a high temperature indicating pyonephritis. It thus may be seen that pyelography is not always a harmless procedure in the presence of an infected kidney, and that it should be used with great caution on any kidney the conservation of which is absolutely indicated. In the same manner, vigorous manipulation of a kidney in the course of nephrectomy for tuberculosis of the kidney may permit the pelvic contents to enter the blood stream and cause postoperative tuberculous septicemia. Another spontaneous pathologic condition which may be the result of excessive pressure within the pelvis of the kidney is acute ureteral obstruction by a calculus, kink or spasm. The colic provoked by any one of these causes often is followed by such symptoms as hematuria, chills and fever, which also may follow artificial distention of the renal pelvis. Thus, the abundant hematuria which in classic theories has been attributed to the lesions caused by the migration of a calculus seems to Hortolomei, Ornstein-Streja and Burghele to be the result of the pyelovenous reflux that occurs during the colic.

Acute pyelonephritis and acute attacks during the course of chronic pyelonephritis may likewise be attributed to massive extension of the kidney due to acute pyelitis through the mechanism of pelvic extravasation, proof of which is found in the histopathologic appearance of the lesions, the suddenness and gravity of the acute attacks and the rapidity of extension of the inflammatory process. In so-called essential hematuria there is, most of all, evidence of the pathogenic rôle played by pyelovenous reflux. The primary cause of such reflux may lie in nephroptosis or ureteral spasm, both of which have been observed repeatedly to be associated with hematuria. Chyluria similarly may follow pyelolymphatic reflux by a mechanism of the same type. Finally, perirenal hydronephrosis and spontaneous perirenal hematoma may be accounted for by the mechanism of perivascular extravasation. The fact that such hematomas repeatedly have been observed to be preceded by violent renal colic inclines the authors to adopt the same pathogenic explanation. After the production of extravasation and pyelovenous reflux the hemorrhage may continue and produce a subcapsular hematoma.

Many of these hypotheses are the result of logical deductions, but since they are based on experimental evidence they should be confirmed by laboratory and clinical study of patients.

*Polycystic Diseases.*—Goldstein<sup>18</sup> described a new surgical treatment of polycystic kidneys:

This consists of extraperitoneal exposure of the kidney, freeing the organ, decapsulation where possible, incision and excision of the cysts, nephrostomy,

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18. Goldstein, A. E.: A New Surgical Procedure for Treatment of Polycystic Kidneys, *J. Urol.* **34**:536 (Dec.) 1935.

nephropexy, the establishment of a temporary nephrocutaneous non-urinary fistulous tract, and finally the subsequent puncturing of reformed or large cysts. When the abdominal route is employed . . . a pararectus high Gibson incision is made down to the peritoneum. The peritoneum is then pushed medially, exposing the kidney with its fatty layers. It is then freed laterally on each side. The true capsule is incised lengthwise, opening some of the cysts. Numerous large cysts are then opened, excising the walls of many of them. As many as possible of the cysts are drained. After this procedure the kidney cortex is then split from one pole to the other. . . . With the kidney split, more cysts are drained with the needle and syringe. Hemorrhage is not marked. The medial half of the longitudinal portion of the kidney is then sutured to all layers of tissue above and medial to it, the peritoneum being pushed downward and inward. The other half of the longitudinal split portion is treated likewise. The wound is closed with interrupted plain catgut sutures.

At the end of operation the kidney is well immobilized, and the split cortical portion is exposed. The split halves are approximated to the skin edges. . . . Laterally, the same situation exists, except that the kidney is not in apposition to the peritoneum. This leaves the organ free so that the cysts may be punctured with a needle and syringe under visualization at will, a procedure which is carried out after healing.

The operation is indicated: when there is gradual reduction in the function of the kidneys with nausea, vomiting, weakness and uremic manifestations; when there is pain due to an increase in the size of the cysts and a consequent increase in the size of the kidneys; when there is hematuria resulting from rupture of the enlarged cysts into the calices with anemia and weakness; as a last resort in the treatment of polycystic disease accompanied with uremia and coma.

The immediate result of this operation in a case reported by Goldstein was reduction in the size of the kidney with relief from pain, nausea and vomiting, which had been present for eight months before the patient sought medical attention. The fistulous tract on the left side was kept open for two and a half months, after which it was permitted to "granulate over." The patient gained 16 pounds (7.3 Kg.) and was so well that he returned to work. Seven months later he began to have pain in the right abdominal region with nausea; the right kidney became larger. Immediately following operation on the right kidney, the nausea subsided. He remained well for several months, and then the pain in the right abdominal region returned. The right kidney was again found to be enlarged. The cysts on the left side were again punctured, with relief from symptoms. Goldstein expressed the opinion that the two operations and the subsequent puncturing of the cysts on the left side saved the life of a patient who was in a desperate condition.

*Replacement Lipomatosis.*—Lieberthal<sup>19</sup> said that comparative pathologic studies have demonstrated that replacement lipomatosis is an

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19. Lieberthal, F.: Perirenal and Peripelvic Fibrolipomatosis: Their Relation to Replacement Lipomatosis of Kidney, Surg., Gynec. & Obst. **61**:794 (Dec.) 1935.

advanced form of peripelvic fibrolipomatosis, which accompanies any chronic suppurative process in the kidney to some degree. This condition is a combination of hyperplasia and fibrosis of the peripelvic fat, occurring in response to chronic suppuration and contracture of the kidney. In the advanced form of the disease, the peripelvic fat appears as though it had undergone an extensive active proliferation and as though it had crowded into the renal substance and produced pressure atrophy and destruction of the latter. Histologic examination of the renal tissue usually reveals pyelonephritic contracture and traces of the preceding suppurative process.

All portions of the pathologic adipose tissue in replacement lipomatosis of the kidney are directly continuous with the remainder of the peripelvic fat, and they are definitely demarcated from the renal tissue proper. The development of replacement lipomatosis depends on the presence in the kidney for a period of years of a chronic low grade suppurative process. The circumstances that tend to maintain such a process are those of long continued incomplete obstruction to the outflow of urine from the renal pelvis. Replacement lipomatosis of the kidney must be distinguished from neoplasms of the perirenal and peripelvic fat, of the fibrous capsule of the kidney and of the renal substance. It should not be confused with liposis, which is an entirely different pathologic entity.

*Perinephric Abscess.*—Rusche and Bacon<sup>20</sup> said that the significant signs and symptoms of perinephric abscess are pain and tenderness in the costo-iliac space, fever, leukocytosis and roentgenologic findings. Frequently, such an abscess has failed to produce the usual symptoms before operation. Diseases involving adjacent structures have presented all the symptoms and findings of a perinephric abscess. All regional structures must be considered in the differential diagnosis. The operation for this lesion is exploratory. Early operation when perinephric suppuration is suspected is a justifiable procedure.

Rusche and Bacon reported 10 cases in which the condition was diagnosed as perinephric abscess. Operation was performed for perinephric abscess in 9 of these cases. The final diagnoses were: appendical abscess in 2 cases, osteomyelitis of a rib in 1 case, osteomyelitis of a rib and vertebrae in 1 case, osteomyelitis of a vertebra in 1 case, ruptured hydronephrosis in 1 case, ruptured aneurysm of the abdominal aorta in 1 case, retroperitoneal abscess containing a toothpick in 1 case, retroperitoneal abscess following perforation of a cancerous bowel in 1 case. In 1 case no pathologic condition was found.

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20. Rusche, C. F., and Bacon, S. K.: Unusual Conditions Simulating Perinephric Abscess with Report of Ten Cases, *J. Urol.* **34**:504 (Dec.) 1935.



*Nephrotomy.*—Martin and Bruneton<sup>21</sup> described a simple method of suturing used by Marion to secure hemostasis after nephrotomy. The method, which is known as “perirenal subcapsular encirclement,” consists in running catgut of a large size (no. 4) completely around the incised kidney, underneath the capsule, without penetrating the organ itself, by passing the curved needle in and out through the capsule until each catgut thread has encircled the kidney like a gathering string in a garment.

Before beginning this reefing, provisional hemostasis is obtained by means of a compress which is passed, in the form of a loop, under the pedicle by means of a curved clamp. The first catgut thread is inserted, by means of a straight needle, under the lower pole of the kidney, through a buttonhole made in the capsule; the double catgut thread is then basted through under the capsule, the two ends being temporarily left free, one at each margin of the incision. Six catgut threads are similarly drawn around the kidney, about 2 to 3 cm. apart and parallel to one another, until the entire length of the kidney has been so surrounded. One should be careful to avoid the pedicle. The ends are not tied until all the threads have been inserted and until a drain has been placed in the lower third of the pelvis of the kidney; the threads are then drawn together and the ends tied successively in such a manner as to assure perfect coaptation of the two flaps; the threads cannot slip during the reefing, because they are held by their buttonholes. After all the ends have been tied the compress is removed, and the neatly bound kidney is replaced in its bed. Before suturing the lumbar muscles, a few moments should be allowed to elapse in order to make certain that hemostasis is actually complete. If there is any oozing, the insertion of an extra catgut thread will usually stop it.

Marion said that coarse catgut threads will more simply and more easily produce hemostasis equal to that which Lowsley effects with bands of catgut ribbon. They can be drawn tight because of their suppleness, and by pulling all of them progressively and successively there is no risk of their breaking; breaking may occur if an infected kidney is sutured by transfixion. The use of fat to tampon the renal breach has not been found necessary. The principal indication for the method is to secure hemostasis after section of the parenchyma of the kidney for the removal of one or more calculi, especially if infection is present.

*Transabdominal Nephrectomy.*—Rathbun<sup>22</sup> said that the most common indication for transabdominal extraperitoneal nephrectomy is a large tumor of the kidney. The reasons for this type of approach are the necessity for more room and better exposure, the desirability of an early approach to, and control of, the vascular pedicle, and the impor-

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21. Martin, R. H., and Bruneton, Jacques: Un nouveau procédé d'hémostase dans la néphrotomie: Le cerclage sous-capsulaire périrénal, *J. d'uro.* **39**:550 (June) 1935.

22. Rathbun, N. P.: Transabdominal Extraperitoneal Nephrectomy, *Tr. Am. A. Genito-Urin. Surgeons* **28**:139 (June) 1935.

tance of securing the pedicle before there is any extensive manipulation of the kidney. The main disadvantage of this approach is the occasional difficulty of keeping the intestines out of the operative field. This sometimes involves a considerable degree of mauling of the intestine with resulting increase in the shock involved at the time of operation and increased likelihood of postoperative ileus with its attending discomfort and risk.

It is Rathbun's belief that when the kidneys are unusually large, particularly if there is excessive enlargement of the upper pole, transabdominal extraperitoneal nephrectomy is so difficult as to be practically impossible of execution. When the kidney is large, if the anterior approach is selected, the transperitoneal route is preferable. In this operation the pararenal fascia is usually automatically separated when the outer leaf of the mesocolon is divided. The colon may then be readily displaced toward the midline. If more room is needed, this can be obtained by rolling the liver downward and inward, which is readily done as an intraperitoneal procedure.

#### URETER

*Calculus.*—François<sup>23</sup> said that ureteral calculus is serious since it is able to destroy the kidney rapidly by obstruction, dilation and infection. A roentgenogram and a urogram should be made to determine the exact situation of the stone in the ureter. It is necessary to know definitely that the shadow represents a calculus in the ureter, and it is necessary to determine the dimensions of the stone and the changes which have occurred in the affected ureter and the condition of the associated kidney, that is, whether there is dilation or infection, and the function of this kidney.

François reported a series of 53 cases of stone in the ureter. In 16 (30 per cent) of these cases, the stones were passed naturally after cystoscopic procedures such as insertion of an inlying ureteral catheter, injection of glycerin or oil of cajuput, the use of Livermore's dilator, ureteral sounds and dilating bougies, the use of ureteral forceps and fulguration of the orifice of the ureter. In a case in which there was recurrence of stone it was necessary to perform a ureterolithotomy. Extraperitoneal ureterolithotomy or nephrectomy was performed in 35 cases. Ureterolithotomy was performed in 32 cases, and nephrectomy for pyonephrosis was performed 3 times. Nephrectomy for pyonephrosis resulting from ureteral fistula was necessary in 2 cases. There was no immediate mortality. In 3 cases there was recurrence of ureteral stone. The functional value of the associated kidney, which was deter-

23. François, Jules: Diagnostic et traitement des calculs de l'uretère, J. d'urol. 39:219 (March) 1935.

mined in 18 cases, varied from no decrease in function to complete dysfunction. The functional improvement after operation was verified in 11 cases. The function returned to normal in 2 cases and showed marked improvement in 6 cases. Infection of the associated kidney was noted in 15 cases; it disappeared spontaneously after removal of the calculus in 3 cases, and after changing the acidity of the urine and the use of urinary antiseptics and pelvic lavage in 3 other cases. It was decreased in 2 instances by the same therapy. In 2 cases there were stones in both ureters.

*Obstruction.*—Henline<sup>24</sup> reported 66 cases in which the presence of noncalculous ureteropelvic obstruction was proved by operation. The cases occurred in 37 males and 29 females. The average age of the patients was 32 years. The right side was affected in 40 patients, and the left, in 27. Forty-four patients had infection. The complications were nephroptosis in 9 cases, infantile kidney in 1, double kidney in 2, single kidney in 2. In 11 cases the condition was bilateral. The phenol-sulfonphthalein test for function of the kidney on the affected side revealed no function in 32 patients, 50 per cent or less of the normal function in 26 and more than 50 per cent of the normal function in 9. This test is inaccurate in determining the function of the renal parenchyma in hydronephrosis. Neither comparative determination of the amount of urea in the urine from the kidney nor intravenous urography gives an accurate index of renal function in hydronephrosis. In most cases, hydronephrosis results from obstruction at the ureteropelvic junction. The cause of the obstruction should be sought while the kidney occupies its normal position in the loin, rather than after it is delivered.

The cause of obstruction found at operation was stricture in 31 cases, aberrant vessels in 29, fibrous bands or adhesions in 18, high ureteropelvic insertion in 6 and a combination of these causes in 17. Palpation of the ureteropelvic junction may reveal increased density from muscular hypertrophy and hence a decrease in the size of the lumen of the ureter, or a stricture.

Nephrectomy was necessary in 45 cases; lysis and severing of the aberrant vessels or fibrous bands, with nephropexy, was done in 16, and plastic operations were performed in 6. The latter type of procedure may be successful in the presence of an infected kidney. Aberrant vessels (unless large) may be safely divided. In 29 cases, anomalous vessels were sectioned without demonstrable ill effect. If the obstruction is outside the ureter and is the result of fibrous bands, adhesions

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24. Henline, R. B.: The Cause and Treatment of Non-Calculous Ureteropelvic Obstructions, with Report of Sixty-Six Operated Cases, *J. Urol.* **34**:584 (Dec.) 1935.

and aberrant vessels, satisfactory results are obtained by complete lysis of the renal pelvis and upper part of the ureter, combined with nephropexy. The Fenger operation is not satisfactory. In the presence of strictures and high insertion of the ureter, reimplantation of the ureter into the lowest portion of the renal pelvis gave satisfactory results in 61 cases. There were 2 deaths; 2 patients required secondary nephrectomy, and 1 of these was improved. Although the function of the kidney has improved and the size of the pelvis decreased, neither has returned to normal in this series of cases.

*Anomalies.*—Randall and Campbell<sup>25</sup> reported 2 cases in which an obstructive nephropathy with pyonephrosis was caused by the passage of the ureter completely around the vena cava in its descent to the bony pelvis. Three cases in which this anomaly was found at necropsy and a case in which it was found at operation have been reported in the literature. The anomalous embryologic development responsible for this condition is described. A new and highly suggestive clinical sign, which should aid in the preoperative diagnosis of this condition, is the peculiar position that the ureteral catheter occupies in relation to the vertebral column when lateral roentgenograms are taken. In the normal position the ureter is seen to fall away from the spinal column, but when it passes behind the vena cava it is observed to be impinged against the lower lumbar vertebrae.

*Ureterocele.*—Moukharinsky<sup>26</sup> submitted a report on the pathogenesis of ureterocele, based on the study of 8 cases observed personally and a review of the literature. Three examples cited demonstrate satisfactorily that ureterocele, even though bilateral, may not be congenital but acquired as the result of traumatism or inflammation. In none of the cases reported were there any anomalies of formation. According to some authors, ureterocele is found chiefly in persons of asthenic type, with nephroptosis and visceroptosis. The asthenic constitution was present in 1 of the patients and nephroptosis in 4. In 1 patient the ureterocele was bilateral; nephroptosis of the right kidney and a kink of the upper portion of the ureter also were present on the same side. In another patient there was a ureterocele on the left side, with prolapse of the mucosa of the right ureter, while on the right side there was nephroptosis without any anomaly of the direction of the ureter. The interest here lies in the combination of a ureterocele on one side, on which the kidney was in place, and prolapse of the mucosa on the other side, on which the nephroptosis was found.

25. Randall, Alexander, and Campbell, E. W.: Anomalous Relationship of the Right Ureter to the Vena Cava, *J. Urol.* **34**:565 (Dec.) 1935.

26. Moukharinsky, A.: De l'urétérocèle, *J. d'urol.* **38**:1 (July) 1934.

After contraction of the ureteral orifice, many authors assume that a secondary condition is necessary to provoke a ureterocele, and a great many theories have arisen; their multiplicity, however, is sufficient proof of their insufficiency. Among other erroneous statements is the assertion that the ureter, in its upper portion above the ureterocele, is necessarily subjected to dilation. Ureterograms in a number of cases in which there was no dilation have shown that the ureter was of normal size following electrocoagulation. After electrocoagulation, incision or even resection of the part of the ureter that has descended toward the urethra, the ureterocele disappears; sometimes it remains as a pad of mucosa, and the ureter and the surrounding walls resume their faculty of contraction. As for the lower portion of the ureterocele, the dilation may remain after coagulation, according to the persistence or disappearance of changes occurring in its walls. Thus, in the case of a ureterocele of large size which contained 8 calculi examination a year and a half after coagulation and evacuation of the calculi revealed dilation of the vesical end of the ureter of such extent that an attempt at catheterization failed, the catheter coiling into a ring within the persistent sac.

If one holds to the theory that weakness of the walls of the bladder or of the general system is a necessary condition for the formation of a ureterocele, one will find it impossible to explain the return to normal of the lower end of the ureter with reference to the surrounding walls of the bladder in cases in which this occurs.

The theory accepted by the author with reference to the mode of formation of a ureterocele is that of Federoff: Whether congenital or acquired, the ureterocele presents as its most marked characteristic the contraction or nonpatency of the ureteral orifice. As the result of this contraction the upper portions of the ureter are dilated by the urine; the ureter then becomes cystic and begins to swell within the bladder. As the dilation and the swelling gradually increase the end of the ureter may descend (in females) even through the urethra and come out into view. A swelling of such a kind will, of and by itself, form an obstacle to evacuation of the urine from the kidneys and will lead to dilation and atony of the ureter throughout its entire course and to dilation of the renal pelvis.

As regards treatment, there is not much controversy except in the case in which the cyst is so large as to fill the bladder or the case in which it descends through the urethra. In the former case, some authors recommend only endovesical coagulation or, if that is impracticable, coagulation within the sectioned bladder. Others differentiate between cysts with thin, transparent walls and those with thick walls, and advise the surgical treatment for the latter. Most authors approve of resection of the strangulated portion if the ureterocele has prolapsed to the

exterior. But some, for example Gottlieb, would use coagulation in all cases on the ground that resection leaves a gaping orifice behind, creating conditions favorable to reflux and to ascending infection. This is a point which Moukharinsky regards as rather well founded, especially in view of the fact that coagulation leaves undisturbed the ganglions innervating the lower parts of the ureter, the conservation of which is of great importance for maintaining the equilibrium of the muscular work which the bladder has to perform. But there is only one answer to the question whether every ureterocele ought to receive treatment: The condition is a pathologic one which, if left to itself, is likely to become the source of grave disturbances higher up in the urinary tract. The frequency of ureterocele is much greater than a review of the literature indicates, as the subject does not seem to have received the attention it deserves in the archives of clinics.

*Dilatation.*—Thomas and Barton<sup>27</sup> stated that congenital anomalies of the genito-urinary tract occur frequently in infants and children and predispose to pathologic conditions of this system. Since the advent of excretion urography and the more frequent examination of children by the urologist, the number of congenital anomalies which have been reported has increased. The incidence of congenital bilateral idiopathic dilatation of the ureters in children is greater than the present reports indicate. If such dilatation is bilateral it is a serious condition which is not improved by plastic surgery. If it is unilateral, nephro-ureterectomy offers a satisfactory result.

#### BLADDER

*Tumors.*—Smith<sup>28</sup> offered an analysis of a series of 150 cases of tumor of the bladder, which were observed personally. The data on 100 of these cases were fairly complete, including the end-results; the information on the remaining 50 was insufficient to permit a complete study. The cases occurred in 94 men and 56 women. The ages of the patients ranged from 29 to 84 years. The incidence among females (37.3 per cent) was relatively high compared with that in the large series reported by the Carcinoma Registry (23.75 per cent). The average age of the patients who had the papillary variety of tumor was 52.8 years; 41 per cent of them were less than 50 years of age. The average age of those who had the infiltrating type was 61.2 years; only 15 per cent were less than 50 years of age. These figures indicate that

27. Thomas, G. J., and Barton, J. C.: The Rôle of Congenital Anomalies in the Production of Urologic Conditions in Children, with Special Mention of Congenital Idiopathic Dilatation of the Ureter, *Tr. Am. A. Genito-Urin. Surgeons* 28:231 (June) 1935.

28. Smith, G. G.: The Treatment of Bladder Tumors, *Pennsylvania M. J.* 38:569 (May) 1935.

the average age of patients who have tumor of a high grade of malignancy is greater than that of patients who have tumor of a low grade of malignancy.

There were 41 cases of the papillary variety of tumor and 59 of the infiltrating variety.

There were 27 cases of single papillary tumor and 14 of multiple papillary tumor. In 3 cases of single tumor the diagnosis was simple papilloma, and in 6, papillary or epidermoid carcinoma; 18 cases were without pathologic diagnosis. Of the 27 patients with single tumor, a number of whom probably had papillary carcinoma, 6 had the growth removed through the open bladder. One of these, in whom epidermoid carcinoma arose from the orifice of the bladder, had twelve gold radon seeds, each containing 2 millicuries of radon, implanted. Of the other 5 patients, 1 died of carcinoma of the bladder in nine months; 4 are living three, six, eight, and nine years, respectively, after operation. Three of the latter have had no recurrence, and the fourth has not been examined.

Twenty-one patients who had single papillary tumor were treated cystoscopically by electrocoagulation; in 3 of them, one or two gold radon seeds were implanted in the wall of the bladder at the base of the tumor. These 3 patients are living and without recurrence seven months, ten months and two years, respectively, after treatment. Eighteen patients were treated by cystoscopic electrocoagulation alone; 4 of these patients are dead, and 14 are living. Of the 14 patients now living, 7 have been free from recurrence for from two to twelve years. Seven have had recurrences, chiefly in the first two or three years after destruction of the original growth, but are still alive. Six of these are now free from the growth, but small velvety patches are developing in the bladder of the other patient faster than they can be destroyed. One patient had a recurrence after eleven years; another, after seven years.

Multiple papillary tumor occurred in 14 patients; in 4 the growth was diagnosed as papilloma, in 5 as papillary carcinoma and in 1 as squamous cell carcinoma; in 4 the tumor was not diagnosed. Eleven were treated through the open bladder, 3 by coagulation and radium and 8 by electrocoagulation alone. Of the 3 patients treated with radium, 1 died in two years of carcinoma of the bladder, 1 has lived six years without recurrence, and 1, ten years with but one recurrence, six months after operation. Of the 8 patients treated by electrocoagulation alone, 1 died of carcinoma of the bladder twenty months later, and 1 died of the same disease two years after the treatment. Two have lived four and five years, respectively, without recurrence; 3 have lived three, four and seven years, respectively, with recurrence in the first two years.

The end-result bears no demonstrable relation to the presence or absence of malignancy in the tumor. The prognosis for multiple tumor is definitely worse than that for single tumor. Deaths from carcinoma in the group of patients with single tumor were 8 per cent as contrasted with 21 per cent in the group with multiple tumor. Obstinate recurring tumor was encountered in only 1 patient in each group.

Two of the 59 patients who had infiltrating tumor were treated by implantation of radium seeds through the cystoscope. In both the tumor was ulcerated, sessile and single. In one, the growth appeared to be controlled eight months after treatment, and in the other, fifteen months after treatment. Twenty-eight patients were treated by implantation of radium through the open bladder. Five patients, who appear to have been cured, have lived without recurrence for from three to fifteen years, respectively. Cystotomy and electrocoagulation were performed in 4 patients. Three of these are dead. One lived two months and died of pyelonephritis. Two died of carcinoma of the bladder within six months and three years, respectively, after operation. The fourth is living five years after operation, but the growth has evidently extended beyond the bladder into the pelvic tissues. Resection of the wall of the bladder was done in 13 patients. Seven of these have died, 3 postoperatively. Four died of carcinoma six months, nine months, two and a half years, and three and a half years, respectively, after operation. Six patients have lived for five months, one year, five years, five years, eight years and ten years, respectively, after operation.

Total cystectomy was done in 10 patients. In 6 of these the ureters were implanted in the bowel; in 3 they were implanted in the skin. Bilateral nephrostomy was done in 1 patient. Three of these patients are living and apparently well two, eighteen and seven months, respectively, after cystectomy and ureterostomy, and one, eight months after cystectomy and uretero-enterostomy. In 5 others diversion of the urinary stream was done; in 3 of these it was only a palliative measure. Two patients were subjected to ureterostomy; each lived five months. Three were subjected to uretero-enterostomy; they lived only five days, two weeks and six weeks, respectively. In the entire group of 59 patients with infiltrating carcinoma, 6 died as a result of local recurrence who might have been saved by cystectomy. All of these patients were treated by cystotomy and implantation of radium.

Rabson<sup>29</sup> reported 2 cases of atypical carcinoma of the urinary bladder simulating myosarcoma. In a review of the literature it was found that sarcoma of the bladder is approximately three times as common among men as among women. The incidence, according to age,

29. Rabson, S. M.: Atypical Carcinoma of the Urinary Bladder Simulating Myosarcoma: Report of Two Cases and Review of the Literature. *J. Urol.* **34**:638 (Dec.) 1935.



although irregular, is almost the same for both sexes. After the first ten years of life, the incidence is low.

The problem of etiology in the study of the neoplasms has been discussed by Rabson. In cases of sarcoma of the bladder occurring early in life, 8 in infants less than 1 year of age, the tumor unquestionably was embryogenetic. Cases of sarcoma have been reported in workers in the aniline industries. Experimental work has been done with the coal tar products. Bauer treated fistulous bladders in animals with these chemicals, and Perlman and Staehle injected coal tar products subcutaneously, but all reported the production of only benign fibro-epithelioma. Bilharziasis was seen with sarcoma and with carcinoma by Ferguson. Kartulis also recorded the association of sarcoma with bilharziasis. Chronic inflammation may result in the appearance of lymphoid tissue in the wall of the bladder even though normally none is present.

The symptoms of sarcoma of the bladder are similar to those of carcinoma of the same organ, both in variety and degree of severity. Dysuria, hematuria and retention of urine are prominent. The site of the tumor is usually on the lateral or posterior wall or on the base, including the vesical neck. The superior and anterior walls are involved about half as often as the portions just mentioned. Multiple occurrence, considered the result of metastasis or of direct spread, has been reported observed in 32 patients, whereas a single mass has been recorded in 145.

The neoplastic masses may or may not be pedunculate. There was ulceration of the tumor in 56 instances, and in 16 there was not any ulceration. In 20 patients only was the presence of calculi observed. In 1 of these patients there had been an operation for stone twelve years before. There is a definite statement of the absence of calculi in 14 patients. The entire thickness of the wall of the bladder was invaded by the sarcoma in 45 cases, and in 16 there was not complete invasion. Operations, usually partial resection of the bladder, were done in many of the patients, but generally death occurred less than a year and frequently a half year later. Metastases were usually found in regional lymph nodes, although neoplastic masses were also seen in distant lymph nodes. All organs, with the exception of the brain, have been recorded as being the site of metastatic growth.

*Cystectomy.*—Freiberg<sup>30</sup> presented a new method for total urethrocystectomy in the female, which may be the treatment of choice in certain cases of carcinoma of the bladder:

Preliminary lumbar ureterostomy is performed on one ureter and then, usually from one to three weeks later, on the other; the bladder is removed at a third

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30. Freiberg, H. B.: Total Urethro-Cystectomy in the Female—A New Technique, *J. Urol.* **34**:615 (Dec.) 1935.

operation. The patient is placed in the position for lithotomy, after which the vagina is prepared in the routine manner. An incision is made in the anterior wall of the vagina, corresponding to the primary incision of an operation for cystocele. A line of cleavage is started by blunt dissection between the posterior surface of the bladder and the anterior surface of the uterus. With a gauze-covered finger, this dissection is continued backward until the bladder is completely freed from the uterus. The blunt dissection is continued laterally until the inferior surfaces of the lateral vesical ligaments are reached. The primary incision in the wall of the vagina is then carried forward and upward around the external urinary meatus. The urethra is dissected free from its bed, and the dissection is carried anteriorly beneath the pubis until the inferior surface of the pubovesical ligament is reached. With the patient in the same position except for lowering the head of the operating table, a suprapubic incision is made in the median line. The preperitoneal fat and peritoneum are freed from the inner surface of the abdominal wall by blunt dissection. The blunt dissection is continued downward beneath the pubes to the pubovesical ligament. This dissection is simply accomplished since the bladder is empty. The bladder is allowed to remain empty during the entire operative procedure. The pubovesical ligament is then ruptured, thus making the dissection from above continuous with that from below. This dissection is continued laterally for a short distance until the lateral vesical ligaments are reached. The urethra is grasped through the suprapubic wound and pulled anteriorly and upward.

Following this the lateral vesical ligaments, containing the superior and inferior vesical arteries, are isolated. A curved clamp is applied to each lateral vesical ligament, and the ligaments are severed. The urethra and bladder are then dislocated anteriorly as much as the latter is attached only to the peritoneum. The blunt dissection previously started per vagina is continued upward, completely freeing the bladder from the peritoneum and allowing for its removal. After the removal of the bladder the vesical ligaments are ligated with sutures of no. 3 chromic catgut. Two Penrose drains are introduced into the space of Retzius and allowed to extend through the incision in the vagina. The suprapubic wound is closed without drainage. The incision in the vagina is closed around the Penrose drains.

*Tuberculosis.*—Valerio,<sup>31</sup> using as a basis for discussion 2 widely different illustrative cases of primary tuberculosis of the bladder, demonstrated that a great many of the sweeping generalizations made in the literature with reference to this disease are unsound and that every case is more or less individual.

Thus, one of the patients had a hereditary predisposition to tuberculosis, while the other patient had not; one stated that he had no venereal history, while the other stated that he had had a gonorrheal infection six years previously, which allegedly had been cured. Tuberculosis of the bladder is regarded as a disease of early adult life and of youth; the first patient belonged to this age group, but the second was a man of 58 years. Nearly always the bladder is inoculated following tuberculosis of one or both kidneys, and the beginning of the

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31. Valerio, Americo: Sur la tuberculose vésicale primitive, J. d'urol. **38**:530 (Dec.) 1934.

tuberculous lesions of the bladder around the ureteral orifices is considered proof of this. Clinically, there are many exceptions, and among such are the cases under consideration; in neither of these cases was the vesical tuberculosis accompanied by a corresponding tuberculosis in the kidneys.

It should be recalled that it is possible for the bacillus of tuberculosis to localize primarily in the bladder just as in the lungs, ganglions, meninges or peritoneum. When it does, one may speak of urovesical tuberculosis, which proceeds from granulations to caseation and ulceration. But if the bladder is involved following lesions of nearby organs, especially of the kidneys, the involvement may be secondary tuberculous infection of the bladder and the condition should be called "tuberculous urocystitis."

Secondary infections are of great importance from the standpoint of diagnosis, prognosis and treatment since they aggravate primary tuberculosis of the bladder and sometimes render it incurable. In the patients mentioned, who had been treated for years for "pyelonephritis," the tuberculosis of the bladder was primary. Primary tuberculosis of the bladder is of extremely slow evolution, while tuberculous cystitis is of much more rapid development and is more progressive. It is worthy of note that the first patient had complained of urinary disturbances for eight years, and the second had had a similar disturbance for thirty years. Both patients were cured, and the cure has persisted.

The lesions generally begin at the trigon or in the ureterovesical region; but in these 2 patients the ulcers were localized at the cupola and in the left lateral half of the bladder. In one patient the trigon was normal; in the other it was the site of slight grayish granulations; an abscess was forming in one of these. In both patients the ureteral orifices were easily catheterized and were intact.

The most interesting feature in these 2 cases was the fact that for many years the tuberculosis of the bladder had disguised itself as a vesical pyelonephritis, without signs of cystitis; a variety of bacteria had been found in the urine, but the bacillus of tuberculosis had not been recovered. Both patients had presented the enterorenal syndrome; one had harbored *Escherichia coli* in his urine, and the other had harbored enterococci. It is usual for the renal phase to come as the final stage of this syndrome, with or without simultaneous repercussions in the bladder. But in these two patients there was no cystitis; the symptoms were solely those of pyelonephritis. There was no great reduction in the functional capacity of the kidneys, and pyelography revealed nothing abnormal. While the urine did not contain the bacillus of tuberculosis it contained *Staphylococcus albus*, *Staphylococcus aureus*, streptococci and *Micrococcus catarrhalis*. The tendency of ulcerations to heal spontaneously was not observed here inasmuch as the disease

had been of long duration in both cases. Raising the question whether the bacillus of tuberculosis is found in the product of ulcers and in the vesical and renal urine, the author points out the inconsistency of the findings; Colson, for instance, found this organism in the urine of 84 of 88 patients suspected of having the disease, while it was not present in the urine of either of the 2 patients reported on here. The results of the inoculation of guinea-pigs were positive, and cystoscopic examination had already established the diagnosis of vesical tuberculosis.

After this study, one thing is certain, namely, that the conception of renovesical tuberculosis merits a drastic revision from the ground up, in order to get away from worn out aphorisms.

*Resection.*—Harris<sup>32</sup> described the operation of posterior segmental block excision of the neck of the bladder with primary closure, which he considers an improvement over such well recognized operations as cuneiform resection and complete extirpation of the neck of the bladder. After cuneiform resection there is likely to be recurrence of the obstruction. Extirpation of the neck of the bladder has the disadvantages of being unnecessarily extensive and leaving an open raw surface, the bleeding from which is controlled by gauze packing. The operation described by Harris has been performed on 33 patients within the past six years without mortality and, up to the present, without recurrence of obstruction. It is designed for the relief of certain obstructive conditions of the neck of the bladder when there is no gross enlargement of the prostate gland. These conditions include the various types of median bar, or disease of the posterior commissure, and general fibrosis of the prostate. The operation should not be used in the treatment of enlargement of the lateral lobe of the prostate gland, although it will occasionally prove of value if the bladder has to be opened for the treatment of recurrence of obstruction after prostatectomy. In making the selection of the type of operation to be used in relieving obstruction of the neck of the bladder, due regard must be given not only to the actual obstructive condition but also to the possible presence of complications such as calculus or diverticulum of the bladder and gross hypertrophy of the interureteric bar.

Following exposure of the base of the bladder, the tip of the right forefinger should be gradually but firmly inserted through the internal meatus, which frequently in this condition may not yield to any but the firmest and most persistent pressure. Two deep traction sutures are then placed, one on each side, about half way around the dilated rim of the prostate gland. Following this, at least 2 cm. of the hindmost sector is excised; this is done by making two deep parallel vertical incisions, one on each side of the midline, and reaching down to the level of the floor of the prostatic urethra. The intervening lip is then firmly drawn up by

32. Harris, S. H.: Posterior Segmental Block-Excision of the Bladder Neck with Primary Closure, *Brit. J. Surg.* 23:45 (July) 1935.

traction forceps and cut out deeply and cleanly in a transverse direction. The bared base must be carefully examined and, if necessary, trimmed. It is important that no gross fibrous or adenomatous remnants remain. The cross-cut ends of the rim of the prostate gland are next freely undercut on each side to permit their complete retraction. Two deep hemostatic sutures are then passed on each side behind the two traction sutures that were inserted prior to the excision. The hemostatic sutures also serve to turn in, on each side, the bared face of the cross-cut ends, thus eliminating the raw surface. When hemostasis by means of these sutures has been accomplished, "retrigonization" is carried out. "Retrigonization" is the name which Harris has applied to the method of sewing down the apex of the trigon into the prostatic urethra in order to insure freedom from formation of a postoperative ledge after prostatectomy. For this step the point of the needle penetrates the base of the bladder at the deepest part behind the interureteric bar. A no. 22 French rubber catheter is passed through the urethra into the bladder, and its end, including the eye, is cut off after an opening has been made about an inch behind the eye of the catheter. The catheter is suspended in position by a silkworm suture thread. The bladder and the abdominal wounds are completely closed and the silkworm suture is suspended to a small glass rod on the abdomen.

*Incontinence.*—Douglass<sup>33</sup> said that many methods for the treatment of urinary incontinence associated with relaxation of the neck of the bladder have been employed with varying degrees of success. The Kelly method has been the most satisfactory procedure for this type of incontinence and is usually sufficient to produce a cure in the average case of relaxation of the vesical neck. Only small superficial bites may be taken in placing the mattress sutures employed in the Kelly technic; unless extreme care is employed, there is danger of penetrating the mucosa of the bladder, with the danger of the development of a fistula. Douglass suggested a plan whereby the tissues surrounding the neck of the bladder may be thickened sufficiently to permit the plicate sutures to be placed boldly and deeply in order to imbricate more tissue. This is to be effected by the use of superimposed purse-string sutures to reduce the wall of the bladder in the presence of large attenuated cystoceles. The prime purpose of this procedure, however, is to insert a valvelike bunching of tissue at the lower margin of the neck of the bladder. Two superimposed purse-string sutures, approximately 2 cm. in diameter, are placed just anterior to the vesical neck, which is outlined by exerting traction on a de Pezzer catheter placed in the urethra. The first of these sutures is invaginated and tied, and a second purse-string suture is then placed immediately over the first one and likewise invaginated. This narrows the bladder from side to side considerably. Two Kelly's mattress sutures are placed immediately over the superimposed purse-string sutures. Before the mattress sutures

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33. Douglass, Marion: Loss of Urinary Control Associated with Relaxation of the Vesical Neck: A Modified Technique for Its Treatment, *Surg., Gynec. & Obst.* 61:534 (Oct.) 1935.

are tied the de Pezzer catheter is carefully stretched over a stylet and withdrawn. The result of the use of this method was satisfactory.

*Nerve Control.*—Dees and Langworthy,<sup>34</sup> in an experimental study of disturbances of the bladder, cut bilaterally the second, third and fourth posterior sacral roots in 39 female cats. Normal urination no longer occurred, and the bladder showed progressive enlargement until overflow incontinence developed between the fourth and sixth postoperative days. The average capacity of the bladder at this time was 191.7 cc., or four and five-tenths times the average normal capacity. The most marked enlargement was to ten times the original capacity. Urine thereafter never escaped from the bladder except by overflow, and there was no subsequent diminution in the capacity of the organ. The bladder became readily infected, and with the most extensive enlargements hematuria occurred from rupture of capillaries in the vesical mucosa. Attempts to establish automatic micturition by passive emptying of the enlarged bladder or by emptying of the bladder before enlargement occurred were unsuccessful. When vesical pressures were recorded no waves of contraction of the pubovesical muscles occurred. There was increased resistance to passive emptying of the bladder. There was no apparent pain or discomfort attributable to vesical distention. Obstipation was marked; the cats became toxic, and the average period of survival after operation was sixteen and six-tenths days.

The abdominal sympathetic chains and hypogastric nerves were removed from 10 animals after the bladder had enlarged following section of posterior sacral roots. Five of these animals died soon after operation. In the 5 surviving animals the bladders eventually emptied automatically and efficiently. Waves of contraction of the bladder appeared when pressures were recorded; the pressure at which the vesical sphincter relaxed became lowered, and the urine, if infected, became clear. One cat survived for five months; the others, for an average of thirty-four days.

*Fistula.*—Lahey<sup>35</sup> presented a method of performing extraperitoneal implantation of ureters in the sigmoid and colon. Although it is applicable only in a limited number of cases, it is so safe and simple that it may prove useful to other surgeons.

An incision of the right rectus is made, and the parietal peritoneum is wiped back as for a ureterotomy. The ureter is then freed and cut close to the bladder; the upper end is now ready for implantation. A small opening in the parietal peritoneum, about 5 cm. in length, is made. The redundant sigmoid is pulled into

34. Dees, J. E., and Langworthy, O. R.: An Experimental Study of Bladder Disturbances Analogous to Those of *Tabes Dorsalis*, *J. Urol.* **34**:359 (Nov.) 1935.

35. Lahey, F. H., in discussion on papers by A. G. Brenizer, W. E. Lower, H. W. Cave and G. R. Livermore, *Am. J. Surg.* **28**:268 (May) 1935.

the peritoneal opening. Only a portion of the wall of the intestine is pulled into the opening, and the lumen is not obstructed. This portion is sutured into the opening and is thereby made completely extraperitoneal. A Coffey no. 2 transplantation may then be done. If a leak occurs, it can be only extraperitoneal. This operation should not be performed on a woman who may become pregnant, as in pregnancy complications may result from the displacement of the ureter and the fixation of the sigmoid.

*(To be continued)*

## CONGENITAL DEFECTS OF FEMUR, FIBULA AND TIBIA

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The question of congenital deformities and defects of the extremities is attractive because of the richness of different morphologic manifestations; it is difficult when it comes to the systematic grouping of observations, and it is extremely embarrassing when etiology is concerned. It seems that with all the scientific armamentarium of modern physicians, they are approaching the problem merely from another side and have not yet succeeded much more in detecting the underlying cause than had the observers of many hundred years ago, who interpreted the various monsters as *lusus naturae*. Nature, or a great vital force, in incalculable mood, enjoys and diverts itself by producing the most abstruse forms. The more modern conceptions are more mechanistic, and the thin amniotic membrane especially has frequently been accused of being responsible for the development of congenital deformities, either by inflammatory adhesions or simply by decreased amount of amniotic fluid. No doubt for a number of cases such an explanation is adequate and satisfactory, but in most instances, it seems rather that endogenous factors are at work. Simple morphologic study has failed to throw light on the inner mechanism of development of congenital deformities, and new attempts will have to be undertaken by experimental biologists. The field is still entirely open.

I report here a number of instances of congenital deformities of the lower extremity, mainly affecting the femur and the fibula. I have tried to arrange the cases so that it becomes evident that congenital defects, of the femur or the fibula, for instance, as a rule cannot be classified individually, but that they are most commonly associated with other deformities. It will be easy to show that most of the patients with congenital defects of the femur have other deformities of the same extremity, and it is rather doubtful whether it is advisable to make the discrimination simply from the largest bone affected. If one reviews a greater amount of material, one gains the certain impression that there are fluent passages from hypoplastic development of the extremity,

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which can be considered as isolated, proportionate dwarfism of the limb, to true deformity due to defects in the skeleton. This fact alone points toward an intrinsic disturbance of growth of the extremity and not toward external factors, such as amniotic constriction or adhesions.

#### CONGENITAL SHORTENING OF THE LOWER EXTREMITY WITH PRESERVATION OF PROPORTIONS: THREE CASES

CASE 1.—The patient was a 3 year old girl. Shortness of the left leg was noted at birth. Development was normal. No other deformities occurred in the



Fig. 1 (case 1).—Congenital shortening of the lower extremity, with hypoplasia of the fibula (upper epiphysis not yet developed). The anteroposterior roentgenogram of the left foot shows marked hypoplasia of the fourth metatarsal bone.

family. Moderate valgus of the left knee was present, with external rotation of the tibia. Roentgenograms showed congenital shortness of the entire left lower extremity without more marked deformity. All the bones were evenly hypoplastic with the exception of the fibula, which was relatively shorter than the tibia and of which the upper epiphysis was not yet developed. The fourth metatarsal bone was less than half its normal size, and the toe was retracted.

CASE 2.—The patient was a 10 month old boy with a family history of shortness of the right foot in the paternal grandfather and an aunt. No gross deformity was present. There were congenital shortness of the right lower extremity and syndactylism of the second and third toes of the right foot, with moderate varus of the knee. Roentgenograms showed hypoplasia of the limb, involving all bones equally.

CASE 3.—The patient was a 1 year old boy who had been born with a short right leg. He had only three toes on the right foot. No other deformities had occurred in the family. The shortness at gross inspection seemed to involve the thigh and the leg equally; on measurement, however, the latter was shown to be

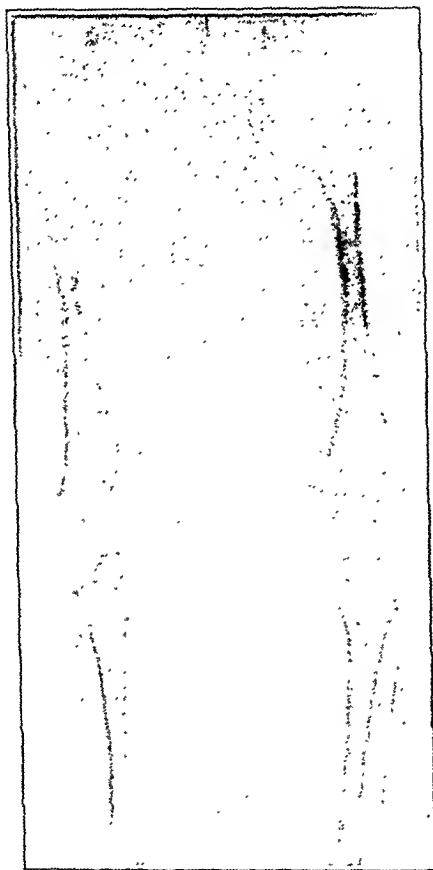


Fig. 2 (case 2).—Proportionate shortening of the right lower extremity.

more affected. Roentgenograms showed hypoplasia of the right lower extremity with a total absence of the fibula; only two inner metatarsal bones and three toes were developed.

These three cases form one group, having in common the hypoplastic development of one extremity. However, there were different degrees of involvement, which besides causing uniform retardation of growth led to suppression of certain portions of the distal part of the limb. The mildest form seems to be the lack of differentiation of the toes, resulting in syndactylism (case 2), brachydactyly (case 1) due to

maldevelopment of the metatarsal bone or hypodactyly due to absence of the lateral toes and the fibula (case 3). The proportion between the thigh and the leg is maintained, although it seems that with the suppression of certain parts of the skeleton the harmonic development of the entire extremity becomes disturbed and the part most affected does not keep pace with the less involved portion. It is thus possible that the proportion between the thigh and the leg, which in the first years of life may be normal, may gradually become changed as the function

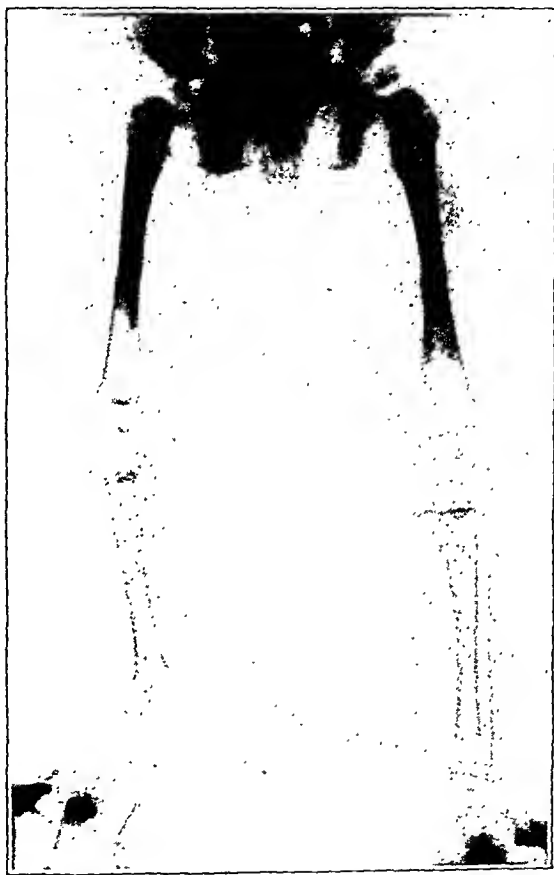


Fig. 3 (case 3).—Shortening of the right lower extremity, with total absence of the fibula. Only two metatarsal bones have developed.

of the extremity is interfered with by the skeletal defect. There can, however, be no doubt that the instances of congenital shortening have to form the point of starting. They are most likely to direct attention toward a disturbance of growth of the extremity by intrinsic factors. However, as so little is known about the factors underlying normal growth, the question is even more difficult if pathologic growth occurs. It may give a slightly better understanding to consider congenital shortening of one extremity as a partial proportionate dwarfism of the body.

Disturbance of the function of the endocrine glands is entirely out of the question. It is a "nanosomia primordialis," based most likely entirely on constitutional factors. One has to figure on an inherited delicate mechanism which controls and maintains the relationship of the different portions of the body. (The term *vis vitalis* has been brought into disrepute by the mechanists, but there still seems to be just that kind of controlling factor.) Cases of hemigigantism and especially of its crossed form bear out the theory that the growth of the extremities is dominated by unknown agents which most certainly cannot be external and mechanical. Heredity is without doubt of greatest importance, and although it is true that for the congenital



Fig. 4 (case 5).—Maldevelopment of the right femur, with marked coxa vara and shortening.

defects of the lower extremity (femur and fibula) the number of instances of hereditary occurrence is very small, it is sufficient to give heredity preference as an etiologic factor. Among the three patients with congenital shortness there was one (case 3) whose paternal grandfather and an aunt showed also congenital shortness of the right foot without the absence of any part.

I consider now another group of cases in which the congenital shortening of the lower extremity was disproportionate, owing to more shortening either of the thigh or of the leg. They, of course, represent more marked degrees of disturbance of growth frequently com-

bined with extensive defects in the skeleton of the extremity. I start with the defects of the femur.

CONGENITAL SHORTENING OF THE LOWER EXTREMITY WITH LACK  
OF PROPORTION: DEFECTS OF GROWTH OF THE FEMUR

EIGHT CASES

CASE 4.—In a 7 year old girl the left femur was markedly shorter than the right but was not deformed. The knee joint was well developed; the tibia and the fibula were normal. The roentgenograms were discarded.



Fig. 5 (case 6).—Congenital shortening of the right femur, with coxa vara. Anterior subluxation of the knee joint.

CASE 5.—The patient was a 15 month old boy, with 4 inches (10 cm.) of shortening of the right lower extremity, all in the femur. The right knee joint subluxated anteriorly with ease when the child kicked and went back into place with a snapping noise. One sister had bilateral dislocation of the hip. Roentgenograms showed malformation of the femur, with a high degree of coxa vara.

CASE 6.—The patient was a 15 year old girl with 8 inches (20 cm.) of shortening, most of it in the femur. Marked genu valgum was present, with habitual subluxation of the tibia in an anteroposterior direction. Pes equinovagum was present. One cousin had a dislocated hip. Roentgenograms showed hypoplasia of the femur, with coxa vara of about 70 degrees. The greater trochanter formed



Fig. 6 (case 7).—Congenital shortening of the femur, with coxa vara. Micro-patella with genu valgum. Absence of the upper epiphysis of the fibula.

a marked bony prominence and almost touched the ilium. The knee joint was deformed, with a micropatella, anterior subluxation of the tibia and valgus of 35 degrees. The fibula was well developed in the upper end.

CASE 7.—The patient was a 29 year old woman with 7 inches (17.5 cm.) of shortening of the left lower extremity, all in the femur. There was marked knock knee, with the foot in 30 degrees equinus deformity. She walked fairly well with a shoe extension. Roentgenograms showed marked shortening of the femur, with coxa vara of about 100 degrees. The shaft of the femur was straight; the knee joint was deformed; the lateral condyles of the femur and the patella were hypoplastic. The upper epiphysis of the fibula was absent. No pictures of the foot were available.

CASE 8.—The patient was a 6 week old girl with absence of the femur. No other deformities had occurred in the family. Roentgenograms showed complete absence of the femur; the leg bones were of normal length; the upper epiphysis of the tibia was not yet developed; the acetabulum was well shaped. The patient



Fig. 7 (case 8).—Extensive defect of the right femur. Only a portion of the lower epiphysis has developed, and it is synostosed with the upper epiphysis of the tibia.

received an extension brace and was seen again two years later. Roentgenograms at that time showed that a small bony process which corresponded to an under-developed lower epiphysis of the femur extended from the upper epiphysis to the tibia. There was no differentiation of the knee joint, and the acetabulum and leg bones were slightly hypoplastic.

CASE 9.—A 5 year old boy had multiple congenital deformities of the upper and lower extremities. Ectromelia of the upper extremities was present, with absence of the bones of the forearm. He had a lobster claw hand with the thumb and little finger present and the third and fourth fingers fused into one giant finger. He walked unaided despite maldevelopment of both thighs and congenital clubfoot on the left. Umbilical hernia was present. No other deformities had occurred in the family. Roentgenograms showed congenital defects of the femur and the fibula on the right; the upper epiphysis of the tibia formed one piece of bone with a rudimentary lower epiphysis of the femur. There was no differentiation of the

knee joint. On the left, the upper epiphysis of the tibia was separated from the lower epiphysis of the femur, indicating that the knee joint was present, but the lower epiphysis of the femur formed only a spherical bony shadow. The pelvis showed complete absence of acetabular cavities. The tibias were well developed. There was marked equinovarus deformity of the left foot, only four metatarsal bones being present.

CASE 10.—A 13 month old girl had been born at full term by breech presentation. Both upper extremities were stumps without elbows or forearms. The left lower extremity was normal; the right lower extremity was much shortened and externally rotated. Roentgenograms showed an absence of the upper half of the right femur. The pointed end of the diaphysis stuck into the acetabulum, which was shallower than that on the left side. The lower epiphysis of the right femur was fused with the upper epiphysis of the tibia, and there was lack of differentiation of the cavity of the knee joint. No patellar shadow was visible (the bony nucleus was not developed on the left side either). There was shortening of the leg, with equinus position of the foot. Anterior bowing of the tibia in the lower

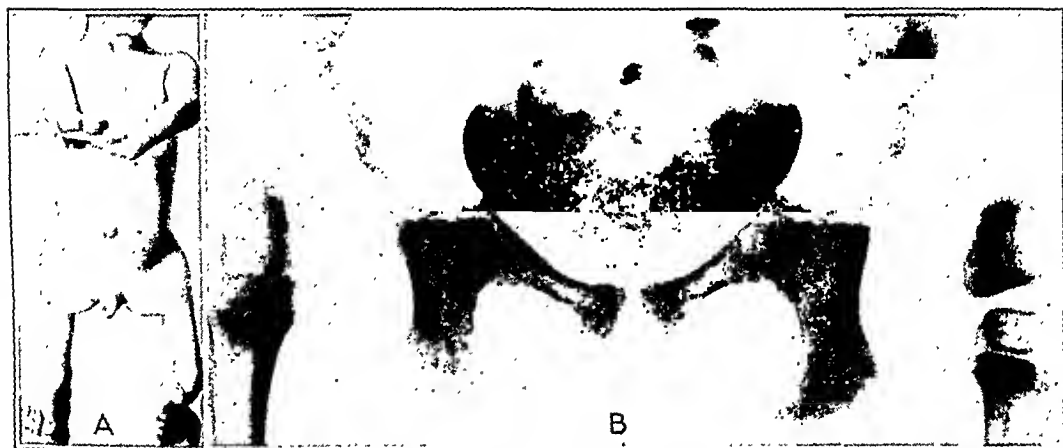


Fig. 8 (case 9).— *A*, congenital deformities of upper and lower extremities. *B*, defects of the femur, with lack of differentiation of the right knee joint. The acetabulums have not developed. The fibulas are absent.

portion of the middle third was present, with complete absence of the fibula. Treatment consisted of the wearing of an extension leg brace with a pelvic girdle.

CASE 11.—The patient was a 14 year old boy, who had been born with a short lower right extremity. The leg and the foot were almost of the same size as those on the left. The muscles of the thigh functioned well. He walked with a prosthesis to compensate for the shortening of 13 inches (33 cm.). Roentgenograms revealed that the right half of the pelvis was considerably underdeveloped; the femur was present only in its upper and lower ends. The upper end was formed by the head and trochanter, which constituted a solid bony mass in varus position; the lower end showed both condyles fairly well shaped, with a good knee joint. The diaphysis was missing. The upper and lower ends were close together but were not in bony union. There was no patella.

The eight cases of this group represent instances of deformity of the lower extremity with the main involvement in the femur. Despite the



small number of cases one can easily recognize certain types of deformity. Case 4 has to be classified as one of real hypoplasia of the femur; that is, the bone was well shaped but diminished in all its dimensions. Here again, one may speak of a partial localized dwarfism of the skeleton. The term hypoplasia of the femur was used by Drehmann and Reiner for a certain form of congenital defect of the femur in which there is a defect or shortness of the diaphysis, whereas



Fig. 9 (case 10).—Congenital defect of the right femur, with absence of the upper half. Synostosis of the lower epiphysis of the femur with the upper epiphysis of the tibia and absence of the patella and fibula are shown.

the upper and lower epiphyses are normally developed. The deformity in case 11 would fall into this group. However, I prefer to use the term hypoplasia congenita femoris only for those conditions in which there is harmonic underdevelopment of the femur without any other defects. Nilsonne expressed doubt as to whether general hypoplasia of the femur should be classified with the congenital defects. I do not share his doubts. He was right in that hypoplasia is not a real defect,

but I conclude from my observations—frequent occurrence of hypoplasia of one bone associated with defects of others—that hypoplasia represents the mildest form of disturbance of growth, which if more marked leads to defects and even to aplasias. Most of the authors who write on congenital defects of the femur consider congenital coxa vara as the mildest form (Drehmann,<sup>1</sup> Reiner,<sup>2</sup> Nilsonne<sup>3</sup>). To a certain extent I agree with this view, but I believe that such a statement has to be accepted with some reservations. There is no doubt that in a number of instances coxa vara represents only a certain form of congenital maldevelopment of the femur, as in cases 5, 6 and 7. In these cases there can be no doubt about the congenital nature of the deformity. The marked shortening of the femur was noted either at the time of



Fig. 10 (case 11).—Congenital defect of the right femur, with absence of the diaphysis and the patella, and a good hip and knee joint.

birth or shortly afterward, but certainly before the child started to walk. However, I should hesitate to accept the deformity in all the cases which come under the heading of congenital coxa vara as intimately related to the congenital defects of the femur. Only deformity which has been recognized clearly before the child started to walk should be classified as congenital coxa vara. Cases of such deformity

1. Drehmann, G.: Ueber angeborene Femurdefekte, *Ztschr. f. orthop. Chir.* 11:220, 1903.

2. Reiner, M.: Ueber den kongenitalen Femurdefekt, *Ztschr. f. orthop. Chir.* 9:544, 1901.

3. Nilsonne, H.: Ueber den kongenitalen Femurdefekt, *Arch. f. Orthop.* 26:138, 1928.

are rare, and there is considerable shortening of the femur. In all the other cases—by far the majority—the condition probably has nothing to do with congenital defect of the femur; it most likely represents some postnatal disturbance of growth in the region of the neck of the femur which, despite many investigations, has not yet been clearly defined.

Drehmann was the first to point out the relation between congenital coxa vara and a certain form of defect of the femur which he called "apparent" defect of the femur. He noted complete absence of the upper end of the femur in a 5 year old boy. At a later examination it was noted that the bony nucleus in the head of the femur had developed, and at the age of 9 years the upper end of the shaft had united with the proximal end of the femur with the formation of a pronounced coxa vara.

It is doubtful whether in cases 5, 6 and 7 the condition was of the same order. There were marked degrees of coxa vara, especially in cases 5 and 6, but the shaft of the femur was straight. In Drehmann's cases of "apparent" defect of the femur the deformity lay mainly in the trochanteric region, and on clinical examination the most prominent portion of the femur was not the greater trochanter but the deformed subtrochanteric region. In my cases it is not unlikely that the deformity was due to a muscle imbalance at the upper end of the femur and around the hip joint. As I shall point out later, one must assume that, owing to influences similar to those from which the skeletal part had suffered in its development, the musculature also was far from being perfectly normal. Besides phylogenetic hereditary factors, it is especially muscle action and weight-bearing which influence and cast the shape of the bone. In cases of congenital deformity of the lower extremity the importance of the musculature has been neglected. Still, it is well known that a disturbance in the equilibrium of the muscles around the hip joint will alter the configuration of the neck of the femur (coxa valga after infantile paralysis or progressive muscular dystrophy); so it may be that a maldeveloped musculature of the femur is responsible for the frequently noted coxa vara in cases of congenital deformity, if the disturbance of ossification alone is not sufficient to explain the deformity.

Cases 8, 9 and 10 are instances of the more common forms of congenital defect of the femur. In most of the cases reported in the literature the upper half of the femur was involved. In my three patients, examined in early childhood, the upper end of the femur was entirely absent (possibly at a later examination the upper end of the femur also became ossified, although there have been autopsies on adults which showed the upper portion of the femur to consist only of a dense strand

of fibrous tissue which connected the acetabular cavity with the upper end of the defective femur). In all three cases (one of bilateral deformity) the lower end of the femur was only of rudimentary development, and in all three the knee joint was not differentiated. The lower part of the femur was synostosed with the upper epiphysis of the tibia. The lower epiphysis of the femur did not resemble the normal shape of the condyles; it was, as a rule, only a small exostosis-like bony prominence. If a part of the diaphysis had already developed, it ended typically pointed (like concentrically atrophic bony fragments) in the soft tissues. In cases of more marked deformity the knee joint may be almost at the level of the hip. In such cases the thigh forms a cone-shaped mass of flesh with fairly good muscle action.

Of interest is case 9, in which the first roentgenogram revealed complete absence of the femur. Two years later a rudimentary lower epiphysis could be observed. From the literature it seems that complete absence of the femur is an extremely rare condition and should not be diagnosed before the tenth year of life, as the diagnosis in early childhood is likely to be erroneous (Reiner<sup>2</sup> and Drehmann<sup>1</sup> did not even include it in their classification). The same seems to be true of absence of the fibula. The ossification in these cases is retarded, and the roentgenogram may change considerably at greater intervals.

A rare condition occurred in case 11. The upper and lower ends of the femur were well developed, the patella was absent and the leg was of the same size as that on the normal side. As a rule, the defect of the femur involves the upper end of the bone; in this case almost a pure defect of the diaphysis was present. There are apparently only two reports of deformity of this kind in the literature: The skeleton of an adult was described by Vrolik<sup>4</sup> and a case in a young child was described by Adrian.<sup>5</sup> In our patient, a 14 year old boy, the condition cannot be considered simply as absence of the diaphysis. The fact that the trochanter and the head of femur were united by a rudimentary neck discloses that at least a small portion of the diaphysis had developed. The condition, however, came close to complete absence of the diaphysis without truly being so.

From my relatively small amount of material it can already be seen that congenital defect of the femur is frequently associated with other deformities of the skeleton, especially of the same extremity, but it is not always true that the more pronounced the defect of the femur the more likely it is that other deformities are present. From the cases in the literature I should say that in about two thirds of the cases

4. Vrolik, quoted by Adrian.<sup>5</sup>

5. Adrian: Ueber kongenitale Humerus- und Femurdefekte, Beitr. z. klin. Chir. 30:401, 1901.

complicating deformities are present. Absence of the patella and absence of the fibula are the most frequently observed complicating deformities. In two of my cases (9 and 10) there was also ectromelia of the upper extremities; in case 9 clubfoot was present on one side; in case 10 there were anterior bowing and shortening of the tibia. In three cases, besides the hypoplasia of the patella, the entire knee joint showed maldevelopment with a valgus deformity and a snapping habitual anterior subluxation of the tibia.

It is of interest that none of my patients with true defect of the femur had evidence in the history that the condition was hereditary, and to my knowledge in none of the cases reported in the literature did the history show other members of the family to be affected by congenital deformities. This is certainly surprising, as milder deformities, such as congenital shortening or even coxa vara congenita, show hereditary or familial occurrence. Still, I believe that in most of the cases the condition is caused by endogenous factors. However, external influences have to be considered in some cases of congenital deformity of the femur, as is shown by the following case:

CASE 12.—The patient was a 3 month old girl, one of twins born at full term by normal delivery. She was born with deformed femurs and with flexion contracture of the left knee. She had umbilical hernia. The twin sister was said to have shown a similar condition; she had a fracture of one femur and died at the age of 3 months. Roentgenograms of the patient showed a marked varus kink in the middle third of the right femur, suggestive of an intra-uterine fracture. The left femur showed similar but less marked bowing at the junction of the upper and the middle third.

It is rather doubtful whether the condition in this case can be classified with the group of congenital defects of the femur. Two cases have been reported in the literature (Lotheissen<sup>6</sup> and Kindl<sup>7</sup>) in which the congenital defect was present in a twin. The same deformity of both femurs, especially of the right, suggests rather an external bending factor due to the crowded uterine cavity. I do not believe that the deformity was due to an intra-uterine fracture in the sense of a traumatic dissolution of the continuity of the bones. This is an extremely doubtful occurrence. It was more likely caused by a continuous bending stress on the soft embryonal bone, due to the abnormal position of the embryo in utero. This case differs from the other cases of congenital deformity of the femur in that one must consider a continuous modeling trauma as the causative factor of the deformity, which means that the deformity did not develop at one time, as in a fracture, but gradually. Such trauma has been accused in the cases of Reiner and

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6. Lotheissen, quoted by Nilssonne.<sup>3</sup>

7. Kindl, quoted by Nilssonne.<sup>3</sup>

Drehmann in the sense that a tight amnion by pull and pressure leads to occlusion of the vessels and impairment of the blood supply to the femur. Reiner, especially, worked out a theory, based on the different vessel systems in the growing femur, to explain the different forms of congenital defect of the femur, but despite the great effort he put into his task, the idea nowadays seems obsolete and far fetched. How-

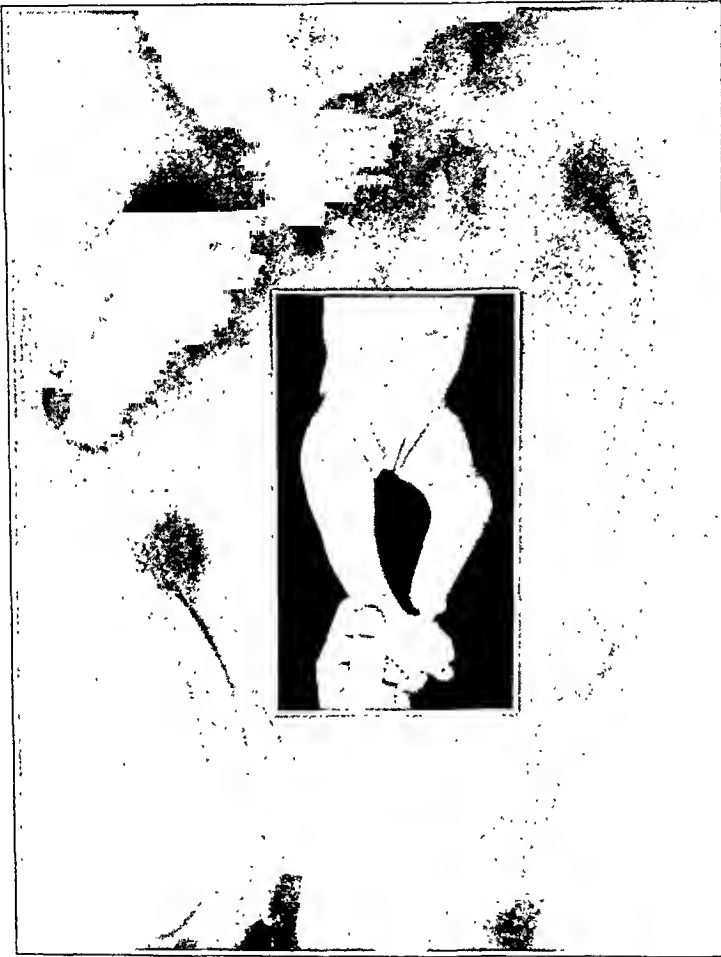


Fig. 11 (case 12).—Congenital deformity of both femurs, probably due to chronic bending stress in utero.

ever, it cannot be denied that especially for the defects in the subtrochanteric region Reiner's theory of occlusion of the vessels is well founded; he already had recognized this part of the femur as a locus minoris resistentiae. In most instances, however, one must consider endogenous factors leading to the disturbance of growth long before ossification begins. Everything points toward an early origin of the

lesion, so that a vitium primae formationis seems to be most likely. Disturbance of vascularization by occlusion of the vessels may be a helpful supposition in some cases, but it can by no means give a full understanding of all the various forms of congenital deformity of the femur. The same is true of intra-uterine trauma, which, even in the mitigated form outlined, can be accepted as an etiologic factor in only a few cases.

CONGENITAL SHORTENING OF THE LOWER EXTREMITY WITH  
LACK OF PROPORTION

*Defects of Growth of Fibula* (Seven Cases).—I now have to consider a group of cases of disproportionate congenital shortness of the lower



Fig. 12 (case 13).—Anteroposterior and lateral views of the right lower extremity, with complete absence of the fibula and anterior bowing of the tibia. Only three toes are present.

extremity, with the main involvement in the bones of the leg. I divide the material into two groups: (a) defects of the fibula and (b) defects of the tibia. As the defects of the femur are often associated with maldevelopment of the other bones of the leg, it is easy to show that the same is true for the defects of the other leg bones which often appear with a congenital maldevelopment of the femur. For this reason it is unsatisfactory to classify the congenital lesions of the lower extremity as defects of the femur and as defects of the fibula or the tibia. I do this only because it is an easier way to present the material.

CASE 13.—The patient was a 10 month old boy, born with a deformed right foot and leg. No other congenital deformities had occurred in the family. Roentgenograms showed complete absence of the fibula, with shortening of the tibia and marked anterior and inward bowing in the middle third. There was reenforcement of the cortex at the concavity. The foot was in a marked equinovalgus position; two lateral toes were missing. The total shortening was  $2\frac{1}{2}$  inches (6.2 cm.). An operation was performed, consisting in lengthening of the achilles tendon, posterior capsulotomy and oblique osteotomy through the tibia at the site

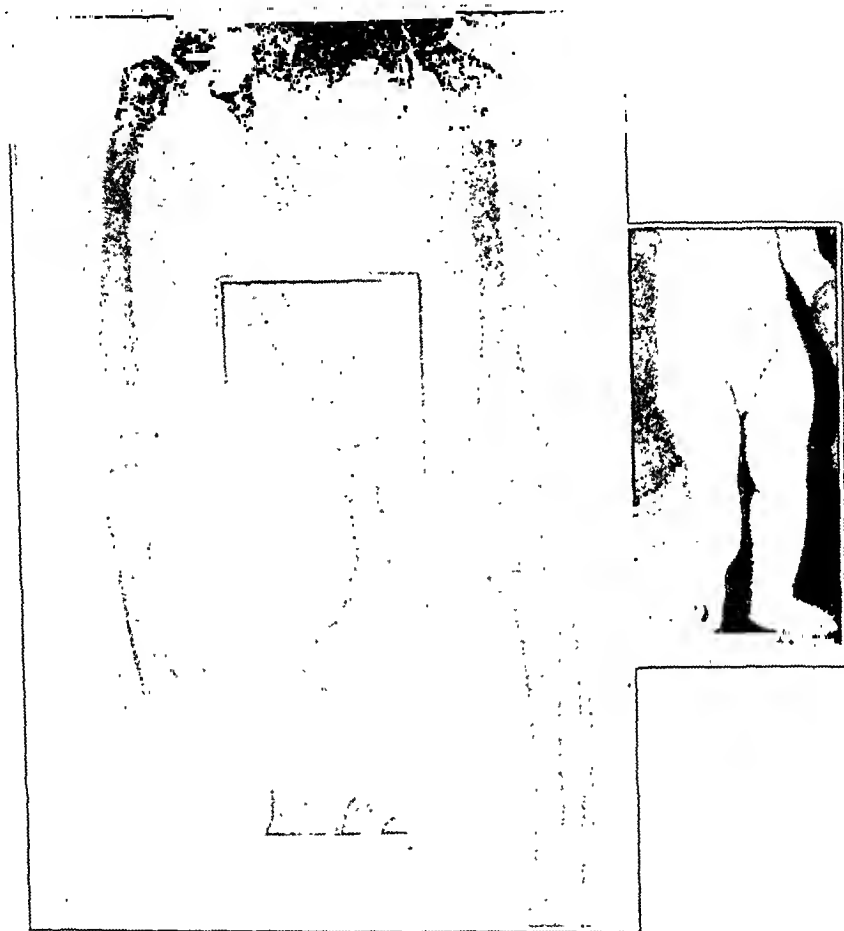


Fig. 13 (case 14).—Disproportionate shortening of the right lower extremity, with complete absence of the fibula and bowing of the tibia.

of deformity. Not much correction was obtained. A peculiar finding was that there was practically no achilles tendon; the muscle fibers extended down to the os calcis. The prosthesis with which the patient walked was satisfactory. Amputation at a later date was considered.

CASE 14.—The patient was a 17 month old boy with about 2 inches (5 cm.) of shortening of the right lower extremity, with anterior bowing of the tibia, marked equinovalgus of the foot and metatarsus varus. When he put his weight on the right foot, he stood on the inner malleolus. Roentgenograms showed complete



absence of the fibula, with shortening and thickening of the right tibia. There was anterior bending in the middle third, with reinforcement of the posterior cortex. The right femur was also considerably shorter than the left, with varus and forward bending at the junction of the upper and the middle third. The bones of the foot were well developed. A wedge osteotomy was performed through the tibia, with correction of the metatarsus varus and lengthening of the achilles tendon. Two years later the shortening amounted to 4 inches (10 cm.), 2 inches (5 cm.) in the femur and 2 inches in the lower part of the leg. An extension brace was applied, and amputation at a later date was considered.

CASE 15.—The patient was a 6 week old boy, born with a short left lower extremity and syndactylism of the fingers. Roentgenograms showed marked shortening of the extremity, with complete absence of the fibula, and only four toes present in the foot. There were considerable anterior bowing of the tibia in the middle third, equinus position of the foot and absence of the astragalus. Multiple deformities were present in the fingers, with hyperphalangism and syndactylism.

CASE 16.—The patient was a 22 year old man, born with a short right lower extremity and clubfoot. Casts were applied in early infancy, and some operations were performed. No treatment had been given since he was 2 years of age. The deformity of the foot was never corrected, and at the age of 8 years it went into a rigid equinus position. He had worn an extension appliance with a false foot. He had pain in the foot and desired amputation.

The total shortening was  $6\frac{3}{4}$  inches (16.8 cm.),  $2\frac{3}{4}$  inches (6.8 cm.) in the femur and 4 inches (10 cm.) in the lower part of the leg. There was good motion in the knee joint but little motion in the ankle joint. The achilles tendon was very tight; the plantar fascia was contracted. Most of the deformity lay in the forepart of the foot. Roentgenograms showed marked shortening of the tibia, which was relatively thick. The lower end was deformed; the joint surface, instead of being horizontal, was in a plane inclined inward, forward and downward. The fibula was present in a hypoplastic stage; it was situated along the lower third of the tibia but did not form the outer malleolus. It still showed division into two epiphyses and one diaphysis. The epiphyseal plates, however, had already disappeared. The foot was markedly deformed; it was kept in extreme equinovalgus position, with adduction of the forepart of the foot and marked cavus. The astragalus had slipped forward; the os calcis showed synostosis with the cuboid bone. The scaphoid bone was wedge-shaped owing to the cavus deformity and was slightly displaced dorsally. The toes and metatarsals were well developed.

CASE 17.—A 4 year old boy had been born with clubfoot. He was treated with casts, and the achilles tendon was lengthened twice. Deformity recurred; especially marked metatarsus varus was present. Roentgenograms showed marked hypoplasia of the fibula, which, however, despite its shortness, resembled closely in shape the normal fibula. There were upper and lower epiphyses, but the lower one did not form the outer malleolus. There was valgus of the heel combined with marked metatarsus varus. The whole right foot was smaller than the left. The bony nucleus of the scaphoid had not yet developed (it was present on the left side). There were only four metatarsal bones; the fourth was thicker than the others and was a combination of two. Webbing of the fourth and fifth toes was present.

CASE 18.—The patient was a 9 year old boy, who had been born with a lobster foot and anterior bowing of the tibia. There was  $3\frac{1}{2}$  inches (8.7 cm.) of shorten-

ing, almost all below the knee. Roentgenograms showed a pronounced deformity of the tibia. It was short, thick and clumsy. The lower epiphyseal plate was very irregular, and the lower epiphysis was small and was represented only by the inner malleolus. The fibula was short and thin and displaced backward and consisted only of a lower epiphysis and a diaphysis. There was no malleolar mortice. The foot was placed laterally to the lower end of both leg bones, which produced a marked valgus kink. It was a typical lobster foot. It seemed that the astragalus



Fig. 14 (case 15).—Congenital shortening of the right lower extremity with complete absence of the fibula and the astragalus.

and the os calcis had fused into a big heel bone. The first and the fifth toe were well developed; there was a rudimentary third toe in the form of a small metatarsus which was in partial bony union with one cuneiform bone. There were another well developed cuneiform bone for the first toe, a cuboid bone and a misshapen scaphoid bone. The other bones of the foot were not developed. The foot was extremely flat.

Amputation at the lower third was performed. The specimen was carefully dissected. Because of the rareness of the deformity, I give here a more detailed description. The foot was very short and lacked completely a longitudinal arch. It was a typical lobster foot, with two outer toes and a rudimentary third toe which had only a small metatarsal bone pointing toward the skin of the dorsum. The inner malleolus formed a large bony prominence at the inner side and reached down to the plantar surface. The inner and outer malleoli were in different frontal planes, at a distance of about 1 inch (2.5 cm.) from each other.

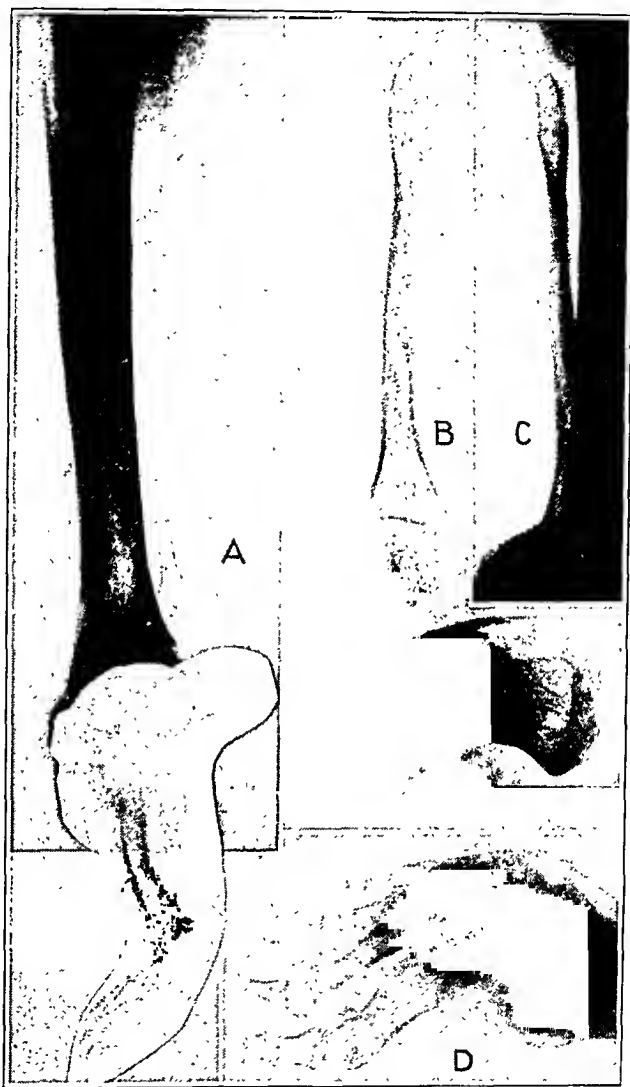


Fig. 15 (case 16).—Congenital hypoplasia of the fibula, with marked cavus deformity of the foot and metatarsus varus. *B* and *C* are lateral and antero-posterior views of the fibula, still showing both epiphyses and the diaphysis.

After removal of the skin a well developed superficial fascia was noted. The muscle groups were all present and were separated from each other by fascial spaces. The gastrocnemius muscle formed a short achilles tendon which was

inserted in the tuber ossis calcis. Both peroneus muscles were present; they left the shaft of the fibula at its lower third and ran to the outer border of the foot. Both were inserted into the tuberosity of the fifth metatarsal bone after passing the dorsal side of the calcaneocuboid joint. The space between the lower third of the fibula and the peroneal tendons was filled with an accessory muscle which formed a muscular bridge between the lower end of the fibula and the os calcis. The extensor group took its origin from the fibula and the intramuscular septum; it formed a muscular leaf of considerable strength, almost in the sagittal plane. Over the dorsum of the ankle the muscle leaf divided into several tendons; one,



Fig. 16 (case 17).—Congenital hypoplasia of the fibula with valgus of the heel and metatarsus varus. Syndactylism of two lateral toes.

inserted at the inner side of the foot, has to be considered as the tibialis anticus. Two tendons went to the first toe; one ended at the metatarsophalangeal joint and the other at the base of the second phalanx. One rather strong tendon was inserted at the base of the rudimentary toe, covered in part by an atrophic extensor digitorum brevis. The most lateral part of the extensor group formed a strong tendon which went to the base of the fifth toe and then ran along its dorsal side to the base of the second phalanx. None of the muscles seemed to have had real action. The flexor group showed good differentiation of the tibialis posterior, flexor hallucis brevis and flexor muscles of the toes. The posterior tibial vessels

and nerve were present; the nerve was considerably flattened where it came to the inner side of the foot. The tibialis posterior muscle ran behind the inner malleolus; its tendon was flat and was inserted on the plantar side of the scaphoid bone. The flexor digitorum communis muscle passed, together with the posterior tibial nerve and vessels, above the abductor muscle of the first toe to the plantar



Fig. 17 (case 18).—Anteroposterior and lateral views of the right leg and foot, showing congenital hypoplasia of the fibula with shortening of the tibia, absence of the astragalus, marked ankle valgus and lobster foot.

side of the foot. Here the tendon divided into two parts, which passed through the tendon sheaths to the first and fifth toes. The short plantar muscles were well developed. The quadratus plantae, lumbricales and practically all the thenar and hypothenar muscles were present.

The dissection of the joint between the tibia, the fibula and the heel bone revealed a strong ligament running from the anteromedial side of the lower end of the tibia to the inner cuneiform bone, reenforcing the articulation. The capsule was thick and tight; it was cut along its entire anterior inferior insertion. Two joint surfaces were present on the medial side of the os calcis for the articulation with the lower end of the fibula and the tibia. They were separated from each other by a capsular septum which came down from the border between the outer malleolus and the lower end of the tibia. The larger joint surface, which extended also on the inner side of the os calcis, was for the tibia. This joint surface was covered by smooth hyaline cartilage, which at the joint margins gradually blended into the thick fibrous tissue of the joint capsule. The inner malleolus had no



Fig. 18 (case 18).—Lobster foot. A detailed description appears in the text.

articulation with the os calcis. The joint with the fibula was smaller and was also covered by hyaline cartilage. The articulation was constructed so that both leg bones, the tibia in an anteromedial position and the fibula in a posterolateral position, articulated with the inner side of the os calcis, which was inclined to the longitudinal axis of the leg. The joint surfaces lay, therefore, in a plane which extended from in front and above and lateral to downward, backward and inward.

CASE 19.—The patient was a  $3\frac{1}{2}$  year old boy, born with deformities on both lower extremities. No other deformities had occurred in the family.

On physical examination marked shortness of the left lower extremity was noted, with valgus deformity of the knee and marked calcaneovalgus of the foot. There was an anterior and inward kink at the junction of the middle and the lower third of the tibia. Directly over the prominent portion of the tibia a small shallow

dimple could be seen in the skin, not adherent to the bone and with normal superficial cutaneous structure. There was no evidence of scar formation. The fibula could not be palpated. The foot showed a marked deformity: Only the first toe was present and fully developed in all its parts. All the other toes were missing. There was only a small tag of skin close to the short outer border of the foot. The os calcis could be palpated; it was in marked equinovalgus position. The skin over its anterior edge showed a thick callus. The achilles tendon was tight. The inner malleolus was prominent, and the foot was flat.



Fig. 19 (case 19).—*A*, complete absence of the fibula, with shortening and bowing of the tibia. *B*, malformation of the feet and marked valgus of the left foot, with shortening of the left lower extremity and genu valgum. *C*, anteroposterior view of the right foot. *D*, anteroposterior view of the left foot.

The right lower extremity was well developed, with the exception of the foot. The lower end of the fibula was displaced backward, with anterior displacement of both peroneal tendons. The foot was narrow and showed only three toes. There was syndactylism of the first and second toes, the latter being hypoplastic. The heel was in slight valgus; the foot was flat. The skin over both lower extremities was free from amniotic scars. There was 2 inches (5 cm.) of shortening of the left leg.

Roentgenograms showed complete absence of the fibula on the left, with marked shortening and some anterior and inward bowing of the tibia, the lower epiphysis of which was very small. There were only two tarsal bones, one of which was the os calcis and the other probably the cuboid bone. The first toe was present, with the metatarsal bone and two phalanges. No other bones were developed. On the right side the tibia and fibula were well developed. The foot showed an astragalus and a deformed os calcis. Three toes were present; the endphalanx of the big toe showed a skeletal syndactylism. The patient was fitted with an extension prosthesis with a pelvic girdle and a free knee. Amputation of the leg at a later date was advised.

CASE 20.—The patient was a 13½ year old girl, born with a short right leg and valgus deformity of the foot. She had been treated in the clinic since the

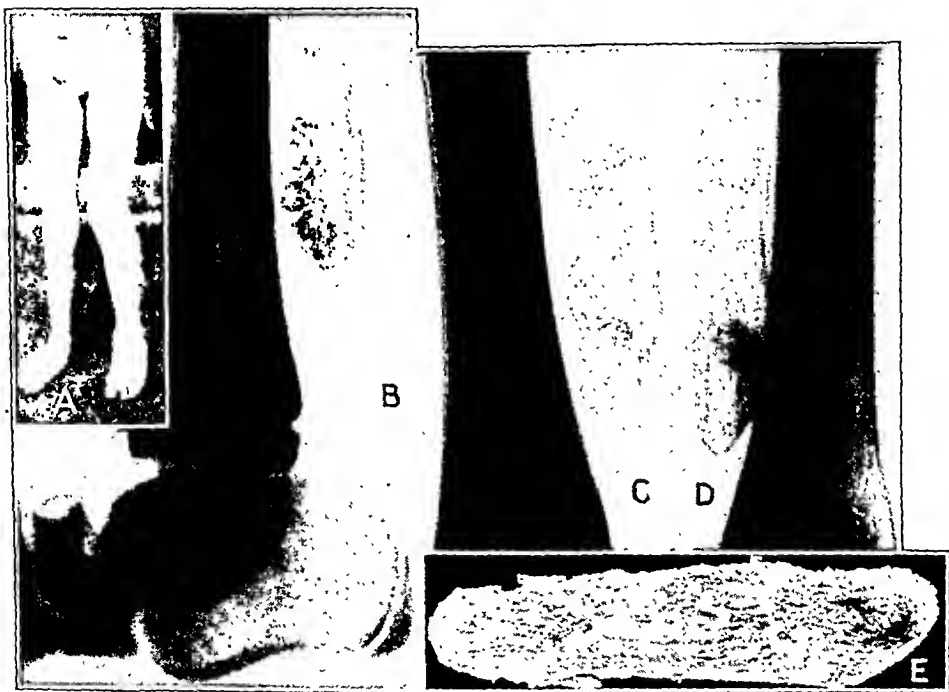


Fig. 20 (case 20).—Congenital hypoplasia of the fibula with shortening of the right leg. *A*, slight genu valgum and marked valgus of the ankle. *B*, lateral view of the ankle region showing irregular calcification of the diaphysis; synostosis between the astragalus and the os calcis. *C* and *D*, anteroposterior and lateral views of the fibula, showing both epiphyses and the diaphysis. *E*, longitudinal section through the specimen, showing the cartilaginous epiphyseal lines, with irregular cartilaginous islands in the diaphysis.

age of 5 weeks by manipulation of the foot and a leather shell. Roentgenograms taken at the age of 2 years showed absence of the fibula. When 1 year old she had a plastic lengthening of the achilles tendon which, at the age of 4 years, had to be repeated, with a posterior capsulotomy. The foot, after that, still showed a tendency to turn to a valgus position, which, however, could be well overcome by an Orr brace. When she was 5 years old, a plastic lengthening of the peroneal tendons was performed. At that time the roentgenograms showed small bony frag-



ments at the lower third of the tibia. They were exposed at the time of operation, and from the lower tip a tendinous band the size of a little finger was noted running down to the os calcis. The lengthening of the peroneal tendons gave little correction; cutting the tendinous band improved the condition moderately. The achilles tendon was also lengthened (for the third time) and a brace was applied. When the patient was 11 years old, the leg was 2 inches (5 cm.) shorter, and there was marked valgus deformity of the heel. The foot was flat, and very little motion was present in the ankle joint. Operative correction of the valgus of the ankle was attempted. No subastragaloid joints were noted; the astragalus was synostosed with the os calcis. The joint surfaces of the tibio-astragaloid joint were almost horizontal instead of convex, thus allowing only a small amount of gliding motion. The Chopart joint line was fused. A Gleich osteotomy was performed through the os calcis, and the fragments were held in apposition by a steel pin. A short leg brace with a valgus strap was applied. The deformity of the foot was well corrected by the operation. When the patient was 13½ years old, the right leg was 3 inches (7.5 cm.) shorter than the left. An operation for lengthening the tibia was performed, and the hypoplastic fibula was entirely removed subperiosteally. A lengthening of 6 cm. was obtained. At the time of writing the child is in a long leg cast.

Roentgenograms taken when the patient was 11 years old showed the lower end of the tibia to be fairly well developed and articulating with the astragalus, which was misshapen, flat and synostosed with the os calcis. There was no subastragaloid joint. The fibula formed a short (2½ inch [6.2 cm.]) ovoid piece of bone, which showed very irregular calcification of its middle half, which corresponded to the diaphysis. This irregular shadow was surrounded by apparently normal periosteal bone, so that one gained the impression that the calcified cartilage of the diaphysis did not undergo normal vascular resorption and that therefore the growth in length was interfered with. There was no external malleolus; the entire fibula lay in soft tissues.

At the age of 13½ there was practically the same relationship of the tibia to the foot. The fibula had increased a little in length (3 inches [7.5 cm.]) and showed definitely two epiphyses and one diaphysis of coarse bony trabeculation. The irregular calcified shadow had disappeared from the diaphysis. The right tibia was well shaped but was much shorter than the left.

I give a detailed gross and microscopic description of the removed hypoplastic fibula because it was the first congenital defect of the fibula which was subjected to careful histologic examination. The fibula represented a more or less cylindric piece of bone 3 inches (7.5 cm.) long and ¾ inch (1.8 cm.) wide, with a crest on the inner side, facing the tibia. The surface showed a smooth, thin cortex, from which the periosteum had been stripped away. There were two division lines of cartilaginous appearance separating the poles from the diaphysis: epiphyseal plates. The upper epiphyseal plate seemed to be complete, the lower was incomplete, with a synostosis between the epiphysis and the diaphysis on the outer side. The whole specimen represented a hypoplastic form of fibula with three centers of ossification, but otherwise the normal shape of the fibula was not reproduced. On a longitudinal section, very coarse spongy bone could be seen, with fatty and hematopoietic bone marrow. The epiphyseal plates were of irregular shape and were frequently interrupted by bone marrow spaces. Many small islands of cartilage which could easily be traced to the epiphyseal plates were included in the diaphysis. In the midline, especially, there was a whole path marked by cartilaginous bodies connecting the most diaphyseal portions of both epiphyseal plates, which means that the epiphyseal lines were not transverse but

more or less funnel-shaped, with the apex toward the center of the diaphysis. It is clear that the cartilaginous islands included in the diaphysis could not be considered simply as fragments of the epiphyseal plates; it is better to consider them as remnants of the cartilaginous, preformed diaphysis. They did not undergo complete enchondral ossification and became included in and separated by the subsequently developing marrow spaces.

On histologic examination the epiphyseal plates were shown to be very irregular, with many degenerative changes in the hyaline cartilage. There was no marked difference between the epiphyseal and the diaphyseal side, present under normal conditions. The lack of difference was due mainly to the fact that even at the diaphyseal side there was little active enchondral ossification. In a few exceptional places the three cardinal stages of enchondral ossification could be noted on the diaphyseal side: (1) proliferation of cartilaginous cells with column formation and (2) preparatory calcification of ground substance, followed by (3) osteoclastic or vascular resorption, with formation of primary spongy bone. The rule, however, is the lack of proliferation of cartilage. There was an irregular zone of calcification present throughout, but this zone rarely became resorbed and replaced by bony tissue. As is typical of a quiescent stage of the process of enchondral ossification, the calcified surface of the epiphyseal disk was covered by a more or less coherent bony lamella. This was a normal finding on the epiphyseal side of the cartilaginous disk, where, as a rule, enchondral ossification was very little active; however, the presence of the bony lamella at the diaphyseal side in a 14 year old person is entirely pathologic. The retardation and small amount of activity of enchondral ossification was also revealed by the absence of inclusion of the calcified cartilage in the bony trabeculae. Normally, the spongy bone close to the epiphyseal plate shows such inclusion, which gradually becomes removed, with static transformation of the primary spongy bone. These inclusions are more frequent the more rapid the enchondral ossification, and vice versa, which means that the better the secondary transformation of bone can keep pace with the enchondral ossification, the quicker they will disappear. The irregular islands of cartilage, which already at gross inspection were observed to be included in the marrow spaces, consisted of mature hyaline cartilage of the same histologic appearance as the cartilage of the epiphyseal disks. Most of these islands were surrounded by a thin bony lamella, and in a few places signs of enchondral ossification were observed, but without proliferation of cartilage cells. The lack of proliferation and the presence of vascular resorption suggested that these cartilaginous islands would ultimately become resorbed completely. The bone marrow in the epiphyses and the diaphyses showed no differences. It was purely fatty, well vascularized and contained cancellous bone of mature lamellar structure. The thin cortical bone on the surface showed considerable lacunar resorption on its periosteal side. The poles of the epiphyses showed the insertion of dense fibrous tissue with the interposition of a zone of calcified fibrous bone.

CASE 21.—The patient was a 14 year old boy with shortening of the right leg and marked valgus of the ankle. The patient took a prize at a baby show when he was 7 months of age. No deformity was noticeable at birth. He had limped ever since he learned to walk. The right foot turned outward; the inner malleolus formed a marked bony prominence. When he was 5 years old, roentgenograms were taken, which showed two areas of rarefaction in the diaphysis of the fibula. The lower focus was explored surgically. A complete pseudo-arthritis of the fibula resulted between the middle and the lower third of the fibula. The leg did not develop well; the shortening increased during five years of observation and amounted at the time of admission to  $1\frac{1}{2}$  inches (3.7 cm.).

Roentgenograms showed the shaft of the fibula to be atrophic, with cystic areas at the junction of the upper and the middle third and of the middle and the lower third. After the exploratory operation a pseudo-arthritis developed at the junction of the middle and the lower third, with concentric atrophy of the ends of the shaft. The entire fibula was relatively short; especially the outer malleolus was high. The tibia was well developed, with the exception of the lower epiphysis, which was small. There was a constant increase of the valgus deformity of the ankle during the various intervals of observation. I consider the condition a relatively mild disturbance of development of the fibula, with pseudo-arthritis of the diaphysis, resulting in shortening of the leg and marked valgus of the ankle.

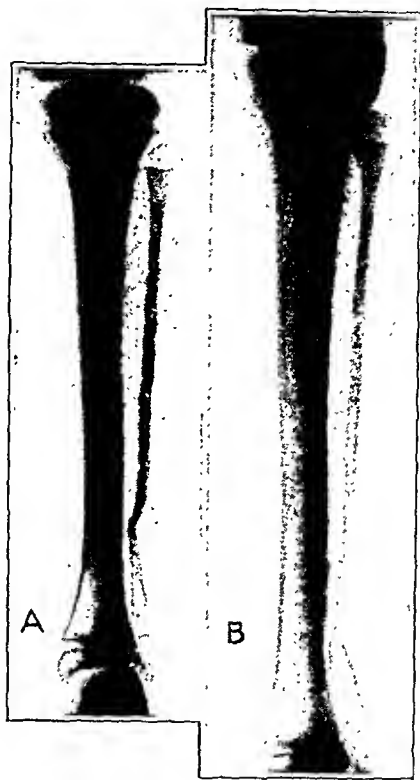


Fig. 21 (case 21).—Congenital hypoplasia of the fibula, with defects in the shaft, and valgus deformity of the ankle. *A*, fracture at the junction of the middle and the lower third (1930). *B*, pseudo-arthritis at the site of the fracture (1935).

To correct the valgus deformity, a supramalleolar wedge osteotomy through the tibia was performed. To stabilize the foot and to prevent recurrence, a heavy bone graft was placed from the lower metaphysis of the fibula to the tibia, so as to cause harmonic growth of the tibia and fibula. To compensate for the shortening of the right leg, the lower epiphysis of the fibula and of the tibia were obliterated on the left. The operation is too recent to judge the result at the time of writing.

#### COMMENT

It is surprising to observe that there have been made several classifications of the congenital defects of the femur (Reiner, Drehmann,

Nilsonne) but that no attempt has been made to classify the different forms of congenital defect of the fibula, although the number of cases reported in the literature is far greater. Reports of more than two hundred cases were collected by Haudek,<sup>8</sup> Scharff<sup>9</sup> and Nutt,<sup>10</sup> whereas Nilsonne's careful review of the literature on congenital defects of the femur disclosed only seventy-two cases, to which he added ten of his own. All the differentiation made of the congenital defects of the fibula is that they are either total or partial, unilateral or bilateral. Still, the survey of a great number of cases in the literature and of my own eleven cases (only one of bilateral deformity) shows clearly that there are certain types which repeat themselves with great regularity. I suggest the following scheme of classification:

*A. Complete Absence of the Fibula.*—This, according to the literature, is by far the most frequently observed form (more than two thirds of all cases reported). This, however, has to be accepted with great care. Most of the cases reported occur in young children, who on clinical and roentgenologic examination may show total absence of the fibula but who a few years later may present a rudimentary fibula in the roentgen picture. In case 20, for instance, the condition was considered as total absence of the fibula until in the fifth year of the life of the patient an irregular bony focus appeared, which gradually developed into a hypoplastic fibula. I am certain that the same would have been true in a great number of cases reported in the literature had the patient been observed longer. Therefore, I believe that the diagnosis of absence of the fibula should not be made before at least the fifth year of life. There are, however, a sufficient number of adults with complete absence so that there cannot be doubt about the occurrence of this condition. It is certain that total absence of the fibula occurs much more frequently than total absence of the femur or the tibia. Absence of the fibula is probably more frequently observed than that of any other long tubular bone.

*B. Partial Absence of the Fibula.*—Considering the ages of the patients whose cases have been reported in the literature and of my own patients, and considering also the possibility of a late partial development of the fibula, I believe that the partial absence of the fibula is as frequent as the total absence, probably even more frequent. The

8. Haudek, M.: Ueber kongenitalen Defekt der Fibula und dessen Verhalten zur sogenannten intrauterinen Fraktur der Tibia, *Ztschr. f. orthop. Chir.* **4**:326, 1896.

9. Scharff, A.: Ueber kongenitalen Defekt der Fibula, *Ztschr. f. orthop. Chir.* **23**:391, 1909.

10. Nutt, J. J.: Congenital Fibular Defects, *Surg., Gynec. & Obst* **37**:475, 1923.

defect may involve different portions; so subdivisions of this group are necessary.

1. Upper part present, lower absent, head of fibula palpable, outer malleolus absent. This defect is either complete absence of the diaphysis and the lower epiphysis, or the upper epiphysis is in connection with a diaphysis of varying length. This deformity seems to be relatively frequent; however, it was not present in any of my cases.

2. Lower part present, upper part absent. The outer malleolus can be palpated in place, or it is hypoplastic and does not help to form a malleolar mortice. It regularly is in connection with the diaphysis, which is thinner and shorter than normal. The upper epiphysis is completely absent. This deformity was present in two of my cases (9 and 18) and probably also in case 1.

3. Upper and lower epiphyses present, diaphysis defective. The whole bone is smaller than normal, the diaphysis is especially thin and interrupted in several places or it ends with two pointed ends near the middle, thus forming a pseudo-arthritis. This deformity is least frequently observed (case 21).

*C. Hypoplasia of Fibula.*—In this condition both the epiphyses and the diaphysis are developed, but the whole bone is hypoplastic and, as a rule, is located along the lower third of the tibia without participation in the formation of the ankle joint. As a rule, these hypoplastic fibulas are considered in the literature as showing an absence of the upper half, which they do not. There are no parts absent. The constant position along the lower third of the tibia instead of in the middle, as one would expect, is most likely due to the more intense growth in length in the upper epiphyseal plate of the tibia, by which the fibula apparently gradually becomes displaced downward. This hypoplastic form is the most interesting type. It either resembles a normal fibula closely in its shape or it is only an ovoid or cylindric piece of bone which has a distinct likeness to the embryonal cartilaginous rodlike preformed fibula. I observed it in three of my cases and found it described exactly in the same form in reports of several other cases in the literature. I had occasion also to examine such a hypoplastic fibula histologically.

From the comparison of the roentgenograms taken at two different periods of development and from gross and histologic examinations I believe that I can conclude that some disturbance in the anlage of the fibula must have taken place. It is impossible to say of what kind this disorder was, but it certainly led to a retardation of growth. Ossification did not take place before the fifth year of life and then occurred in a way which showed clearly that the mainly affected part was the

diaphysis, whereas the ossification of the epiphyses was not greatly disturbed. Histologically, an explanation for the changes could be found in a pathologic process of enchondral ossification, which was abnormal in two phases: There was practically no proliferation of cartilaginous cells and very little vascular resorption. The preparatory calcification, however, was undisturbed. The roentgenograms also revealed that the diaphysis remained in a calcified cartilaginous stage for a long time. The three cardinal phases of enchondral ossification, proliferation of cartilage, preparatory calcification and vascular resorption, have to harmonize for normal growth in length. If proliferation stops but resorption proceeds, the epiphyseal disks disappear, as is the case about the seventeenth year of life. If proliferation and resorption are deficient, the epiphyseal disks may remain open for many years and even throughout life, as is the case in certain forms of true dwarfism and also in nanosomia pituitaria, due to destruction of the anterior lobe of the hypophysis. The histologic changes in my cases compare well with those noted in such cases of dwarfism. The gross appearance of the fibula and the histologic changes, therefore, lead one to believe that one deals with a partial localized dwarfism of the skeleton, affecting the fibula, as I assumed before for certain forms of congenital shortening of the extremity. It seems not only that the ossification of the diaphysis was retarded, but that there also came apparently very quickly an exhaustion of the ossifying power of the diaphysis, which therefore included many cartilaginous islands.

One abnormal structure which has played a certain rôle in the literature is the thick fibrous band which in some cases of absence of the fibula or the femur is observed in place of the bone. Haudek<sup>8</sup> and Krebs<sup>11</sup> considered these bands as proof that the defective bone had a normal anlage but that its further development, to a certain period of embryonal life, was stopped either completely or partially by an external force (amnion). This leads, then, to total or partial congenital absence. From the presence of these fibrous bands the observers concluded that the deformity cannot be a *vitium primae formationis* and that a mechanical force acting in early embryonal life is responsible for it. I do not think that the presence of those fibrous strands has such a decisive importance. I observed this band uniting the lower epiphysis of the dwarflike fibula with the os calcis. As both the epiphyses and the diaphysis had developed, or, in other words, the entire fibula was present although in a hypoplastic stage, the fibrous strand cannot represent the anlage of the fibula disturbed by an external force. It is simply fibrous tissue which in part may be considered as supporting

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11. Krebs, E.: Kasuistische Beiträge zur Kenntnis der kongenitalen Fibula-defekte, *Ztschr. f. orthop. Chir.* **23**:167, 1909.

substance for the musculature, in part simply as connective tissue filling a defect. The same kind of tissue may be encountered between the ends of the bone after extensive resection of the diaphysis, resulting in pseudo-arthritis of the type caused by defect.

*Associated Deformity of Tibia.*—Local dwarfism or hypoplasia of the fibula, however, is only a symptom of a more extensive disturbance of growth affecting the extremity. The defect of the fibula is frequently combined with a characteristic deformity of the tibia and of the foot. I do not intend to give here a complete clinical picture of the congenital defect of the fibula. This has been done already in a number of good articles (Haudek,<sup>8</sup> Scharff,<sup>9</sup> Gaenslen,<sup>12</sup> etc.), but I do want to say a few words about this deformity of the tibia.

It is typically an anterior and sometimes also an inward bowing of the diaphysis, resulting in shortening and thickening of the bone. The kink is either in the middle third or at the junction of the middle and the lower third. Frequently the skin over the apex of the curve shows a small retraction, a dimple.

The deformity of the tibia has been interpreted by many authors as due to an intra-uterine fracture; the dimple was considered as the scarred place where one of the fragments had perforated the skin. Sperling,<sup>13</sup> however, showed conclusively that a trauma of the strength necessary to break an embryonal bone would sooner lead to a rupture of the uterine wall and would be followed rather by abortion than by fracture. Haudek, in an excellent paper, tried to explain all the congenital defects of the extremities, especially that of the fibula, by the assumption of the presence of a narrow amniotic sac, causing localized pull and pressure by adhesion. It has to be admitted that his explanation is able to clear up a number of facts, but it could, so far as I know, never be proved that there is such a thing as a tight amnion interfering with the growth of the extremities or amniotic adhesions leading to bowing of the bones. It has to be conceded that amniotic strangulation and amputation are possible, but that a dimple which is always at more or less the same place should be due to an amniotic adhesion which pulled on the extremity, brought about the bending of the tibia and disappeared, so that nobody has seen one, is more than I can conceive. Haudek examined one of the dimples histologically, and all other writers after him took his interpretation as proof that by pull of an amniotic band a chronic mechanical irritation was exercised on the skin, resulting in a chronic interstitial inflammation, with hyperplasia of the connective

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12. Gaenslen, F. J.: Congenital Defects of Tibia and Fibula, *Am. J. Orthop. Surg.* 12:453, 1915.

13. Sperling: Zur Aetiologie der sogenannten intrauterinen Frakturen, *Arch. f. Orthop.* 1:42, 1903.

tissue and atrophy of the glands and the subcutaneous fat tissue. I cannot follow this argument. The histologic section does not prove anything. I do not think even that a stain of the elastic fibers (which, when the question of a scar in the skin is concerned, is absolutely necessary) would be of great help.

I like to look at these dimples in a different light, basing my conclusions on the fact that they never have been proved to be real scar formations of the integument. They are seen frequently, but in none of the cases was an amniotic band still attached to the dimple. Furthermore, it is not so simple to understand why the supposedly tight and narrow amnion and the amniotic strands should so often interfere with the development of the extremities. It is commonly stated that once they start to develop the extremities form prominences on the surface of the body and on these the diseased amniotic membrane finds points of attachment. But with the same right one could expect insertions of amniotic bands on the head and back which, representing the convex part of the embryo, are closer to the membrane than the extremities. No localized lesion of the head or the back due to amniotic bands has been reported. The extremities, at the time when the adhesions are supposed to do their damaging action (fifth to eighth week of embryonal life), are more or less developing toward the concavity of the bent embryonal body, and there is no reason that they should be predilected points for amniotic adhesions.

If one examines a greater number of these dimples, one finds that they look more or less alike and that they are always related to a prominent portion of the skeleton. In cases in which there is bending of the tibia, the dimple occurs at the apex of the curve; in association with partial absence of the bone it occurs at the pointed end of the diaphysis of the affected bone. They look exactly the same as the dimple which one finds so frequently under normal conditions in the sacrococcygeal region and which is known as the fovea sacrococcygea. This dimple is at that place on the surface of the body where, before its curvature, the caudal end of the vertebral spine was connected with ligamentous connective tissue—the ligamentum caudale. It is possible that, just as the close local relation of a prominent skeletal portion to the embryonic skin results frequently in the formation of a funnel-like depression at this point, a congenital deformity of the extremities may produce a similar dimple. It is not an amniotic band which pulls on the extremity, but it is the deformed skeletal portion which sticks up against the skin and may become adherent to it. Later, when the skin develops in its different layers, especially if the layer of subcutaneous fat tissue appears, it elevates the skin from the adherent and scarred portion, which thus becomes a deeper or shallower dimple, depending on the



more or less marked adhesion of skin to bone. The histologic observations of Haudek<sup>8</sup> speak at least as much in favor of this supposition as of amniotic adhesions. Against amniotic adhesions speaks the fact that the superficial cutaneous structure of shallower dimples is perfectly normal, whereas in cutaneous scars one expects to find typical absence of the small field formation.

But what, if not amniotic adhesion and pressure, brings about the defects of the extremities and especially the characteristic bowing of the tibia? I have already mentioned that I consider more than anything else a faulty anlage of the extremity to lead to a disturbance of growth in a general way, resulting in dwarfism or gigantism of the affected limb, or to act by suppression of one or the other of the centers of ossification, giving rise to congenital defects. The exact mechanism by which the faulty anlage manifests itself, the pathogenesis of congenital deformities, is still unknown; it seems, however, that there is more than a disturbance of ossification. One gains the impression that in cases of more marked deformity the equilibrium which exists under normal conditions between the growth of the soft tissues and that of the skeleton has become disturbed. There can be no doubt that the relation of the musculature to the skeleton is of definite form-shaping influence. I mentioned this fact before, when I spoke of the frequently observed coxa vara associated with congenital defects of the femur. It is more than probable that there is a reciprocity between the growth in length of the skeleton and the expansion of the musculature and other soft tissues. They influence each other by their different stages of physical aggregation. The best example for this existing equilibrium is the fact that the tuberosity of the tibia with the insertion of the quadriceps tendon (patellar ligament) forms a unity with the upper tibial epiphysis, although from a purely morphologic standpoint one would expect the tibial tubercle to form a part of the diaphysis. But by the insertion of the patellar ligament in the epiphysis a bridging of the upper tibial epiphyseal plate by tendon tissue is avoided. The reason for this certainly is that the interstitial growth of the quadriceps tendon could not keep pace with the growth in length of the extremity in both epiphyseal plates around the knee joint. This alone shows how thoughtfully nature tries to keep up the balance between the growth of soft tissues and that of the skeleton. If this balance becomes disturbed, skeletal deformity must be expected.

If one looks up the notes of physical examination of patients with congenital defects of the leg, especially of those with bowing of the tibia, one almost constantly finds the presence of a tight achilles tendon and an equinus position of the foot. This tightness of the tendon seems to be more marked in these patients than in those with other

conditions, for instance, clubfoot. Recurrence following lengthening of the tendon, even if combined with posterior capsulotomy of the tibio-astragaloid joint, seems to be the rule. Operative findings in two of my cases showed that there was practically no tendon tissue but that the fibers of the gastrocnemius muscle were almost inserted into the os calcis, which represents an immature stage of muscle development. As a matter of fact, the clumsy appearance of the thickened and shortened limb, with the marked equinus position of the foot, resembles very closely the youngest stage in the embryonal development of the extremity, long before ossification takes place (the precartilaginous and cartilaginous stage of embryos from 1 to 2 cm. in length). It seems that in these cases not only the growth of the skeleton but that of the soft tissues has suffered, the musculature being much more affected. From the objective findings I conclude that, besides a primary faulty anlage, it may be the disturbed balance of growth in length between the muscles of the calf and the tibia which results in the deformity. If the muscles of the calf do not grow in length in the same amount as the tibia, they will form a tight string on the tibia. The tibia, which at this age is made up of highly plastic material, will have to adapt itself to the shortness of the muscles of the calf either by an anterior bowing or by decreased growth in length, or by both. The decreased growth in length may explain that in some cases of defect of the fibula the tibia is straight but considerably shorter (case 20). It may be straight but show a very clumsy shape (case 17), which is due to lack of differentiation. The bone has preserved its embryonal form to a considerable degree. The disproportion in length between the tibia and the muscles of the calf keeps the foot in its early embryonic equinus position.

The kink of the tibia in the middle third or at the junction of the middle and the lower third corresponds well to the apex of the curve, two fixed points of which are the insertion of the gastrocnemius muscle on the os calcis and the origin on the condyles of the femur, the knee joint being in flexed position (in utero). The kink has thus to be considered as caused by a chronic tension stress exercised on the tibia. From experiments with animals and from clinical observations, especially on bone grafts, it is known that chronic tension stress gradually leads to a zone of transformation of the bone which manifests itself as pseudo-arthritis. It may be that the congenital pseudo-arthritis of the tibia goes back to the same mechanism of imbalance of growth between the bone and the musculature, except that the tension stress in these cases would be more marked. Once the pseudo-arthritis has developed and the fragments are overriding each other, the equinus

position of the foot will correct itself. Therefore, in cases of congenital pseudo-arthritis pes equinus is rather the exception than the rule.

The congenital defect of the fibula is usually combined with an equinovalgus deformity of the foot. This deformity may be combined with a marked metatarsus varus, so that the diagnosis of congenital clubfoot is frequently made. There is lacking, however, the supination of the heel, and the deformity therefore should be considered as a combination of congenital clubfoot with deformity of the ankle due to the defect of the fibula (cases 13, 16 and 17).

The clubfoot component in these cases shows again how intrinsic the disturbance of the development of the extremity is and that endogenous etiologic factors have to be considered first.

The deformity of the ankle in cases of congenital defect of the fibula is often called in the German literature Volkmann's deformity of the ankle joint. Gaenslen introduced the term in the American literature. There does not seem to be anything specific about Volkmann's deformity of the ankle except the pronounced hereditary factor which he observed. He <sup>14</sup> (1873) observed the deformity in father and son; among seventeen members of the last three generations of the same family only ten were not affected. Males and females were evenly represented. Volkmann suggested the name hereditary congenital dislocation of the ankle joints, which was changed later by Bidder <sup>15</sup> to Volkmann's deformity of the ankle, because there is no real dislocation. A number of other cases have been reported, but only in a few was familial occurrence or inheritance of the condition demonstrable (Bidder, Mau <sup>16</sup>). The main factor in the deformity is the aplasia or hypoplasia of the fibula, with absence of the malleolar mortice. In a number of instances the fibula was fairly well developed but was displaced slightly backward and upward.

The deformity of the ankle was present in all my cases but was especially marked in case 18, in which, owing to the lack of the astragalus, complete lateral dislocation of the foot was present. The foot was a typical cleft or lobster foot, a rare condition associated with congenital maldevelopment of the fibula. I found in the literature only the case reported by Spiess.<sup>17</sup> The patient was a 36 year old man with absence of the fibula, shortness and bowing of the tibia and congenital disloca-

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14. Volkmann, R.: Ein Fall von hereditärer kongenitaler Luxation beider Sprunggelenke, *Deutsche Ztschr. f. Chir.* **21**:538, 1873.

15. Bidder, quoted by Mau.<sup>16</sup>

16. Mau, C.: Beitrag zur Volkmannschen Sprunggelenkmisbildung, *Ztschr. f. orthop. Chir.* **48**:434, 1927.

17. Spiess, P.: Ueber kongenitalen Femurdefekt und verwandte Missbildungen, *Arch. f. orthop. u. Unfall-Chir.* **20**:234, 1922.

tion of the hip. The tarsus consisted of only two bones, one of which was the os calcis; the dentate of the other was questionable. Two metatarsal bones and toes were present. In my case a third rudimentary toe was present between the first and the fifth toe.

An even more marked deformity of the foot than that in case 18 was present in case 19, in which only the big toe had developed. There was complete absence of the fibula on the left side, whereas on the right except for posterior displacement of the lower end of the fibula the leg was well developed. Both peroneal tendons ran anteriorly to the external malleolus, and there was marked ankle valgus on both sides. This shows clearly that Volkmann's deformity of the ankle may be associated with complete absence of the fibula as well as with milder developmental errors, as, for instance, a simple backward displacement.

Besides the typical deformity of the ankle, the most common abnormalities of the foot are defects of the two lateral toes. In the cases of milder deformity this defect may be in the form of syndactylism or webbing of the fourth and fifth toes; in more advanced stages there is a fusion of the outer metatarsal bones and finally complete absence of the fifth or of the fourth and fifth toes. Of interest also is the fact that in case 19 the right foot showed syndactylism of the first and second toes. The end-phalanx of the first toe showed skeletal syndactylism, so that it is certain that the whole foot showed lack of differentiation, with complete absence of the two lateral toes. Other deformities, such as absence of tarsal bones and coalescence between the astragalus and the os calcis or between the os calcis and the cuboid are rarer.

In none of my patients with congenital defect of the fibula was inheritance of the condition demonstrable. This, however, should not be taken as proof against a vitium primae formationis and induce one to consider exogenous etiologic factors, such as amniotic constriction. It is a peculiar fact that more pronounced congenital deformities of the extremities are relatively rarely inherited. The milder forms, such as coxa vara, congenital shortness, syndactylism and clubfoot, show by far more frequently hereditary taint. An excellent example of hereditary occurrence of congenital deformity of the lower extremity can be seen in the following group of cases of defects of the tibia.

#### CONGENITAL SHORTENING OF THE LOWER EXTREMITY WITH LACK OF PROPORTION: DEFECTS OF GROWTH OF THE TIBIA

CASE 22.—The patient was a 2½ year old girl with marked deformities of both lower extremities. No other deformities had occurred in the family. Horizontal nystagmus was present. The femurs were well developed. The legs were very short, with angulation of the tibias forward and inward. Both feet were in marked

equinovalgus position. Abnormal movement of the knee joints was present, with subluxation on flexion. There was bilateral dislocation of the hip joints. Roentgenograms showed both hips to be dislocated. The tibias were formed by a clumsy short piece of bone with a sharp anterior edge, which was prominent in its middle. There was a small bony nucleus in the upper epiphysis of each of the tibias and another lateral nucleus in the soft tissue, most likely belonging to a deformed fibula. The bones of the feet showed normal development.

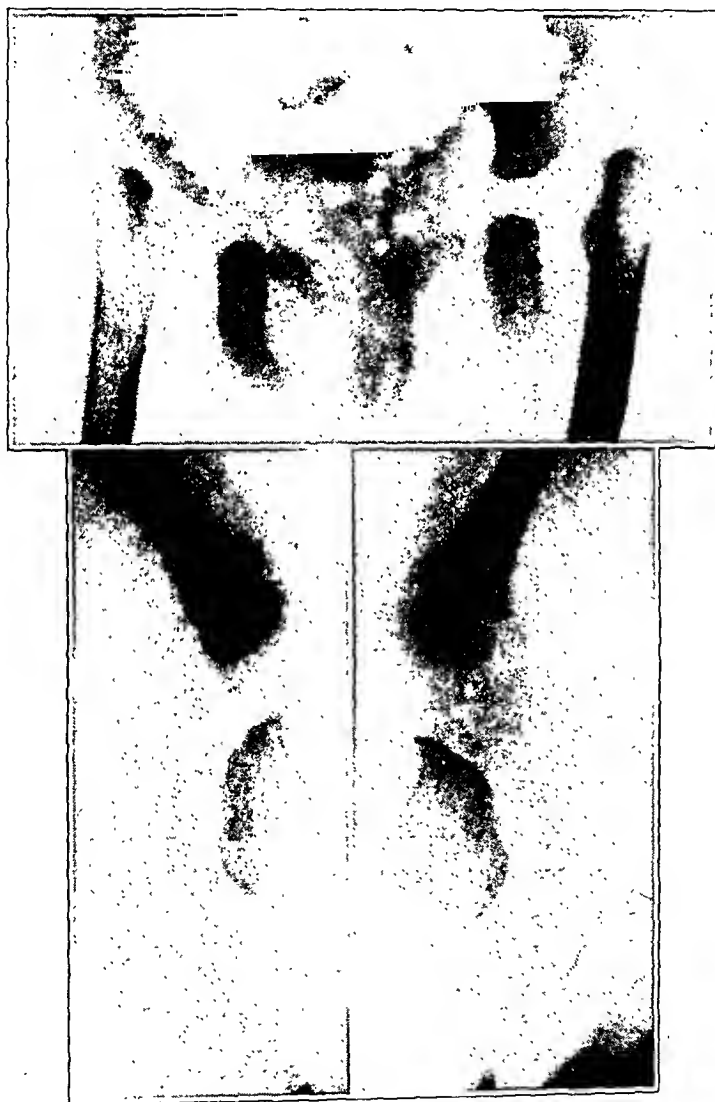


Fig. 22 (case 22).—Congenital dislocation of both hip joints, with deformities of the tibias and absence of the fibulas.

CASE 23.—The patient was a 2 year old boy, born with bilateral clubfoot, especially marked on the left. The inner side of the foot was bent upward, touching the inner side of the leg. A small dimple was present on the lower lateral aspect of the leg. The mother had a lobster hand. The ring finger was absent,

and its metacarpal bone was missing. There was a cleft between the third and the fourth finger, with a web at the base of the metacarpals. Two of three maternal cousins had similar deformities of the feet, and one had a cleft hand. Roentgenograms of the patient showed that in the left leg only the upper half of the tibia had developed; it ended with concentric atrophy. The fibula was well developed and was even thicker than normal. The foot was in extreme equinovarus deformity, but there was no intrinsic pathologic condition in the formation of the bones of the foot. The right tibia was much longer than the left, with

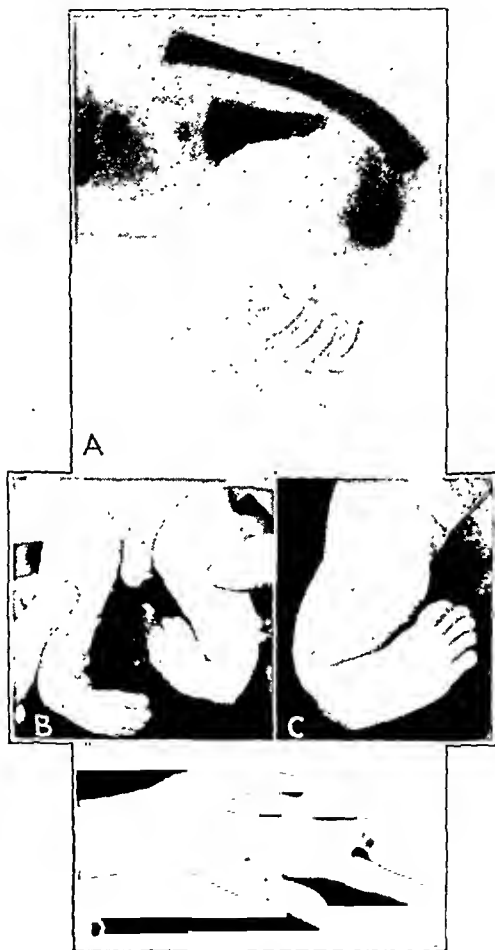


Fig. 23 (cases 23 and 24).—*A*, congenital clubfoot due to absence of the lower half of the tibia. *B*, hypoplasia of the fibula of the patient in case 23. *C*, congenital clubfoot due to absence of the lower half of the tibia in the patient in case 24. *D*, cleft hand of the mother of the patients in cases 23 and 24.

anterior and inward bowing. The fibula was thick and straight and apparently of normal length. The deformity of the foot was less marked; there was no involvement of the toes. Roentgenograms of the hand of the mother showed absence of the fourth metacarpal bone and finger. Some malformation of the carpal bones was present; the hamatum was absent.

*Treatment.*—For the first four months the deformity was treated by manipulation and casts and then by lengthening of the achilles tendon, with posterior capsulotomy. Wedge osteotomy of the fibula on the left foot was performed; the correction obtained was not very good. At the age of  $1\frac{1}{2}$  years the right foot was corrected by lengthening of the achilles tendon and by posterior capsulotomy, lengthening of the inner structures around the ankle joint (Brockman operation), astragalectomy, wedge resection in the calcaneocuboid region, osteotomy of the tibia and surgical union with the fibula to construct a mortice for the ankle joint. Good correction was obtained. Astragalectomy was also performed on the left foot with the Brockman operation with very little correction. Short leg braces were applied; amputation of the left foot was considered for a later date.

CASE 24.—A 6 week old boy, brother of the patient in case 21, had been born with clubfoot on the right and absence of the lower end of the tibia. The fibula was present. A little dimple was present on the outer side, directly over the lower end of the tibia. The inner side of the foot almost touched the inner side of the knee. Roentgenograms showed absence of the lower half of the tibia, with hyperplasia of the fibula which pushed the foot into a marked adduction. The picture corresponded exactly with that on the left side of the patient in case 21. When the patient was 6 months old, the achilles tendon and the inner structures of the region of the ankle were lengthened, and good correction was obtained. Casts and a brace were applied. At the time of writing it is planned to split the lower half of the fibula in a sagittal plane and to transplant the inner half into the tibia in two stages, so as to form a malleolar mortice with growth in length in the transplanted epiphyseal plate.

CASE 25.—The patient was a 1 month old boy, born with clubfoot on the right. No other congenital deformities occurred in the family. The tibia was 1 inch (2.5 cm.) shorter than it should normally have been. Roentgenograms showed absence of the lower epiphysis of the tibia, with considerable shortening. The fibula was of normal length and hyperplastic. The foot showed extreme equinovarus deformity, with marked hypoplastic changes of the big toe, the metatarsal bone of which was merely half the size of that of the second toe.

In the presence of so much hereditary taint as occurred in the two brothers (cases 23 and 24) it is clear that only endogenous factors can be of causative importance for the defect of the tibia. The mother has a typical cleft hand, two maternal cousins have clubfoot, and one has a lobster hand. I deal here with an inherited feebleness of growth of the tibia, which preserved more or less the shape of its precartilaginous and cartilaginous anlagen. In the first and second months of embryonal life the tibia is formed only by a cone-shaped mass. The reason for this lies in the fact that the cartilaginous preformation of the skeleton begins around the knee joint for the lower extremity; it extends the femur upward and the leg bones downward.<sup>18</sup> The thick proximal portions and the pointed distal portions can easily be recognized in the cases in which there is congenital absence of the lower end of the tibia,

18. Bardeen, in Fischel, A.: *Lehrbuch der Entwicklung des Menschen*, Berlin, Julius Springer, 1929, p. 786.

as is also the case with many congenital defects of the femur, which most frequently involve the upper end (the lower end in the tibia). The marked thickness of the fibula also points to this embryonal stage of development. It is clear that this thickness cannot be taken for a compensatory hypertrophy due to the maldevelopment of the tibia, as it is seen also in some cases of osteomyelitic destruction of the tibia. In



Fig. 24 (case 25).—Absence of the lower epiphysis of the tibia, with shortening of the leg. Hyperplasia of the fibula. Hypoplasia of the big toe.

these cases, the hypertrophy of the fibula develops under the stimulus of function, which is absent in the new-born. Up to the third month of life the fibula is evenly developed with the tibia; that is, it is relatively much stronger than the latter. In cases in which there is congenital defect of the tibia, it preserves its early thickness and appears hyperplastic. Thus, despite the fact that the deformities have to be consid-



ered as caused by faulty anlage of the extremities, certain embryonic stages may be recognized in different types of defects.

Better than the defects of the femur, the congenital deformities of the bones of the leg suggest a more extensive disturbance of growth than could be expected from a simple mechanical lesion, such as amniotic constriction. There is a complex disorder, involving the skeleton as well as the soft tissues of the extremities. It seems that the different parts of the extremity are in mutual dependency and that the more affected part will certainly alter the development of the other parts of



Fig. 25 (case 26).—Shortening of the left lower extremity, with posterior and valgus bowing of both leg bones, probably due to chronic bending stress in utero.

the extremity which primarily may have shown normal development. Therefore, there is always participation of the tibia associated with absence of the fibula, to a more or less marked degree, and vice versa, in instances of congenital defect of the tibia, the fibula does not develop to its normal shape but remains at an embryonal stage of hyperplasia. Experiments on young animals with suppression of growth of certain parts of the bones of the lower part of the front or hind legs will probably lead to a better understanding of this mutual dependency.

In the group of cases of congenital deformity of the femur, in which I considered the condition as entirely due to intrinsic factors damaging the development, I reported one case in which intra-uterine trauma was most likely; similarly, I report here a case of congenital deformity of the leg in which the condition also looks more like the result of an intra-uterine bending stress than a *vitium primae formationis*.

CASE 26.—The patient was a 6 month old girl, born with marked calcaneo-valgus. The dorsum of the foot rested on the anterior tibial aspect. The left leg was almost 1 inch (2.5 cm.) shorter than the right and showed lateral and posterior bowing of the tibia and the fibula. Roentgenograms showed marked shortening of the left leg, which was only two-thirds the size of the right. The entire diaphysis, however, had developed. At the junction of the middle and the lower third a kink was present in both bones, with an angle open anteriorly and laterally. No deformity of the foot was present. Treatment was by manipulation and a brace. Considerable improvement was shown within six months.

In this instance of congenital shortening of the leg, some narrowness of the intra-uterine cavity or the amnion sac must have brought the left leg into a pathologic position, resulting in the bending of both bones. The changes in these cases not only look different from real congenital defects but also react in a different way to conservative treatment. In case 13 as well as in case 24 simple conservative means, such as traction, manipulation and the application of a brace, were followed within a short time by marked improvement of the deformity. This shows that the trouble lay in the bone only and that there was no disturbance of the equilibrium of growth of the skeleton and the soft tissues.

# ARRHENOBLASTOMA OF THE OVARY

TESTICULAR ADENOMA TUBULARE

MOSES BEHREND, M.D.

AND

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PHILADELPHIA

To Robert Meyer<sup>1</sup> belongs the credit for the chapter on the special ovarian tumors related to sexual characteristics. Contrary to the old concept that neoplastic cells are nonfunctional, he has pointed out that neoplastic cells may have a specific functional capacity affecting intimately the life of the patient and productive of profound changes in his or her sex life. He grouped these tumors under the following headings: disgerminoma, granulosa cell tumor and arrhenoblastoma.

A disgerminoma occurs either in the testis or in the ovary, and the two types closely resemble each other. The tumor is carcinomatoid and usually results in pseudohermaphroditism. It is said to arise from undifferentiated forms of germinal cells which have lost their faculty for sex determination. It is usually found in young girls presenting hypoplasia and underdevelopment of the genitalia. It may occasionally occur also in boys, and a group of tumors is usually present, lying in a lymphoid stroma.

The second, or feminizing, type—the granulosa cell tumors—may be cylindromatous or folliculomatous (von Kahlden) or may resemble a sarcoma. This tumor causes the secretion of excessive amounts of estrogenic hormones and therefore results in postmenopausal bleeding associated with endometrial hyperplasia. When it occurs in a child it is associated with marked sexual precocity. As the granulosa cell of the true follicles depends for its existence on the fully developed ovum, Meyer stated as his conclusion that it cannot become the forerunner of a granulosa cell tumor. This tumor is said to be derived from an embryologic rest in the medulla of the ovary (Popoff<sup>2</sup>).

The third type, the arrhenoblastoma, arises from undifferentiated germ cells that have retained their potency from epithelium of the testicular anlage or from cell rests in the hilus of the ovary. This type of tumor may cause defeminization: falling out of the hair, atrophy of

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Read in abstract before the Philadelphia Pathological Society.

1. Meyer, Robert: *Tr. Am. Gynec. Soc.* 56:160, 1931.

2. Popoff, N. W.: *Testicular Tubular Adenoma of the Ovary*, *Arch. Path.*

the breasts, shrinkage of the opposite ovary, amenorrhea and sterility. It may be accompanied with signs of masculation: hirsutism and a change in voice (Emil Novak<sup>3</sup>). To be more specific, the rete ovarii and the medullary tubules (the anlage of the gonads) may under abnormal stimulation induce a masculine direction of development.

A subtype in this category of neoplasm is the adenoma tubulare testiculare, described by Pick,<sup>4</sup> to which our tumor belongs. In only a third of the cases does this tumor produce masculation. The degree of masculation may depend on the degree of atypical proliferation of atypical cells. The tumor with a rudimentary tubular structure is more prone to result in masculation (Taylor, Wolfermann and Krock<sup>5</sup>).

#### REPORT OF A CASE

E. O., a widow aged 52, was admitted to the Jewish Hospital on Jan. 28, 1934, with a provisional diagnosis of inguinal hernia on the right side and (?) tumor.

The patient was well until four years before admission, when a lump developed in the right lower quadrant of the abdomen in the inguinal region. It was about the size of a walnut and could be easily replaced. It had gradually increased in size, so that one year before the patient entered the hospital it was irreducible. About three months before her admission it became distinctly noticeable, protruding from the clothing and causing considerable pain and disfigurement. The patient complained of a persistent headache and some edema of the feet. She had never menstruated or had any vaginal discharge. She had been married and had indulged in sexual intercourse, with no lack of libido. There were no pregnancies.

The patient had measles when 6 years old and whooping cough when 12. No operations or accidents had been undergone.

The husband died of heart disease. There was no family history of tuberculosis, cardiac-renal disease, cancer or diabetes.

*Physical Examination.*—The patient was well developed and did not appear acutely or chronically ill. The skin was normal as regards color, texture and warmth. The patient was intelligent and cooperated readily. The voice was feminine in type. No hirsutism was noted.

The hands were normal in development and contour.

The pupils reacted to light and in accommodation and were equal and regular.

The veins of the neck were not distended. The cervical lymph glands were not palpable, and there was no tenderness or rigidity of the muscles. The thyroid gland was not palpable.

The breasts were small and pendulous. The supraclavicular and infraclavicular spaces were marked. Respiration and expansion were good and equal on the two sides. Tactile fremitus and vocal sounds were normal. Percussion revealed no abnormality. No râles were heard. The heart sounds were regular in force and rhythm and of good quality. There were no murmurs.

3. Novak, Emil: *Am. J. Surg.* **23**:595, 1934.

4. Pick: *Beitr. z. klin. Wchmschr.* **17**:502, 1905.

5. Taylor, J. M.; Wolfermann, S. J., and Krock, F.: *Surg., Gynec. & Obst.* **56**:1040, 1933.

The liver and spleen were not palpable. No striae were present. There was no tenderness or rigidity. In the right inguinal region there was a large oval mass. It was not painful but was slightly tender on deep pressure. It was irreducible and fairly heavy. No gurgling was heard, and only slight fluctuation was noted. There was no sign of inflammation or edema.

Vaginal examination revealed a small but lax introitus, admitting two fingers. The vagina was short, measuring  $3\frac{1}{2}$  inches (9 cm.). It was smooth walled and ended blindly. No cervix, uterus, tubes or fornices were palpable. The clitoris was not hypertrophied.

A diagnosis of congenital absence of the uterus was made.

*Operation* (by Dr. Behrend).—Spinal anesthesia was employed. With the patient in the Trendelenburg position an incision was made on the right side about  $\frac{1}{2}$  inch (1.3 cm.) above Poupart's ligament and parallel to it. A large tumor in the right inguinal canal was carefully dissected out and found to be attached



Fig. 1.—Note the vaginal atresia depicted by the opaque solution, the smooth-walled outline of the vagina, the absence of a cervix and the triangular shape of the vagina. The pelvis is of the female type.

to the round ligament. The mass was clamped at the base, ligated and severed distal to the ligature with an electric cautery. The cut ends of the round ligament were sutured to the fascia of the transversalis muscle. The conjoined tendons were sutured to the shelving margin of Poupart's ligament.

*Pathologic Report.*—The mass consisted of an elliptical tumor, the size of a soccer ball, weighing 1,030 Gm. It was firm and on cross-section was seen to be composed of grayish fibers. The central portion of the tumor was of uniform structure. Some sections were more hemorrhagic than others.

Section of the tissue showed a large number of cuboidal epithelial cells having an alveolar arrangement. These glands resembled seminiferous tubules, many of them arranged in cords. The interglandular stroma contained a large amount



Fig. 2.—*A*, photomicrograph of a section of the arrhenoblastoma. Note the orderly arrangement of the epithelial cells about a lumen. There is a marked similarity to seminiferous tubules. *B*, section seen with the oil immersion lens. Note the lack of mitotic figures and the fairly homogeneous character of the cells.

of connective tissue and showed a moderate degree of hyalinization. Some of the fields presented infiltration by solid clusters of cells. No ovarian elements were observed.

The tumor represented a very rare type. According to Pick, such a tumor is derived from ovotestis. However, according to other authorities, it has its origin in the medullary cord, which is the embryologic parent of both the ovary and the testis. In a certain number of cases this type of tumor is associated with pseudohermaphroditism and hirsutism or infantile pelvic organs.

#### COMMENT

The relationship of arrhenoblastoma to intersexuality and pseudohermaphroditism must be very close. Consideration of this relationship also brings forth the question of sex determination. As Novak<sup>6</sup> expressed it, "Is a female a person with a primarily female zygote, or with an ovary, or one with the physical and psychic characters which one associates with a man?" Our case emphasizes that external feminine characteristics are not incompatible with a gonad containing testicular structures. As is well known, the other endocrine glands, such as the adrenal cortex, the pituitary body and the pineal gland, play an auxiliary though important rôle in sex differentiation and may well account for the lack of masculation in some cases of arrhenoblastoma. Thus, in X a case of pseudohermaphroditism in which feminine traits predominate, the only gonads present may be testes. It has also been pointed out that masculation in a person with arrhenoblastoma usually disappears with the removal of the affected ovary unless recurrence takes place on the opposite side (Moots<sup>7</sup>).

#### SUMMARY

A case of testicular adenoma tubulare of the ovary is reported. Masculine features were lacking, but other sexual anomalies were present, such as vaginal atresia, lack of a cervix, a rudimentary uterus and amenorrhea.

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6. Novak, Emil, and Long, J. Herman: Ovarian Tumors Associated with Secondary Sex Changes, *J. A. M. A.* **101**:1057 (Sept. 30) 1933.

7. Moots, C. W.: *Am. J. Obst. & Gynec.* **1**:864, 1921.

# CHRONIC OCCLUSION OF THE PORTAL VEIN

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The following case of chronic occlusion of the portal vein by an old organized and canalized thrombus is reported because (1) few articles have appeared in English on this subject, (2) the condition is rarely diagnosed clinically, usually being mistaken for cirrhosis of the liver, Banti's disease or ulcer of the stomach, and (3) in this case an unsuspected and unusual collateral circulation defeated the anticipated result of a successful splenectomy, which in any other case would have been the logical treatment.

The patient was an obese white woman 34 years of age. Two years before admission to the hospital she vomited about 1 quart (1 liter) of bright red blood. Since that time hematemesis accompanied with epigastric pain which radiated "from the back" had recurred at intervals of from three to four months. She fainted during two of these attacks. The last attack occurred about one month before her admission to the hospital.

At the time of the patient's admission to the hospital physical examination revealed no abnormality except a palpable spleen. She had been married for fifteen years. She had three children who were living and well. There were three miscarriages, the last in 1927 during an attack of influenza. In June 1927 the appendix and a "pns tube" were removed, and the perineum was repaired. In 1930 the patient noted bleeding from the umbilicus during menstruation. This was relieved by a plastic operation in 1931, at which time the uterus was amputated, and the cervix was repaired. The surgeon stated that at operation "a bloody jelly-like substance was spread over the genital organs" in an amount sufficient to fill his hands.

Roentgenograms of the gastro-intestinal tract were normal except for some shadows in the right upper quadrant of the abdomen which were suggestive of gallstones. The blood count showed: red blood cells, from 4,900,000 to 4,520,000; leukocytes, 5,700, and platelets, from 101,000 to 104,000. The bleeding time was three minutes, and the icterus index was 13.4. The Wassermann and Kahn tests of the blood were negative. The urine was normal.

The final clinical diagnosis was thrombocytopenic purpura, splenomegaly and gallstones.

On April 2, 1935, two weeks after the patient's first entry into the hospital, the spleen was removed. The operative notes were as follows: "The spleen is about double its normal size and weighs 500 Gm. or more. Old adhesions to the outer wall and diaphragm are highly vascular. The pedicle is short and contains enormous veins. The appearance of the splenic surface suggests old perisplenitis. The liver shows evidence of old periphepatitis, the right lobe being held to the

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In a section inside the hilus of the liver (fig. 3) there was a rich plexus of vessels which varied greatly in size and in the thickness of their walls. It was not possible to trace the outlines of the original branch of the portal vein in this section. Among the blood channels and vessels were numerous cross-sections of nerves. Above and to the right of the center was a focus of necrosis and lymphocytic infiltration. Along the lower left margin were several groups of proliferated bile ducts.

Figure 4 is a section of a triad located more deeply in the liver. Blood vessels were not as numerous as in sections nearer the hilus, but they were somewhat more abundant than normal.

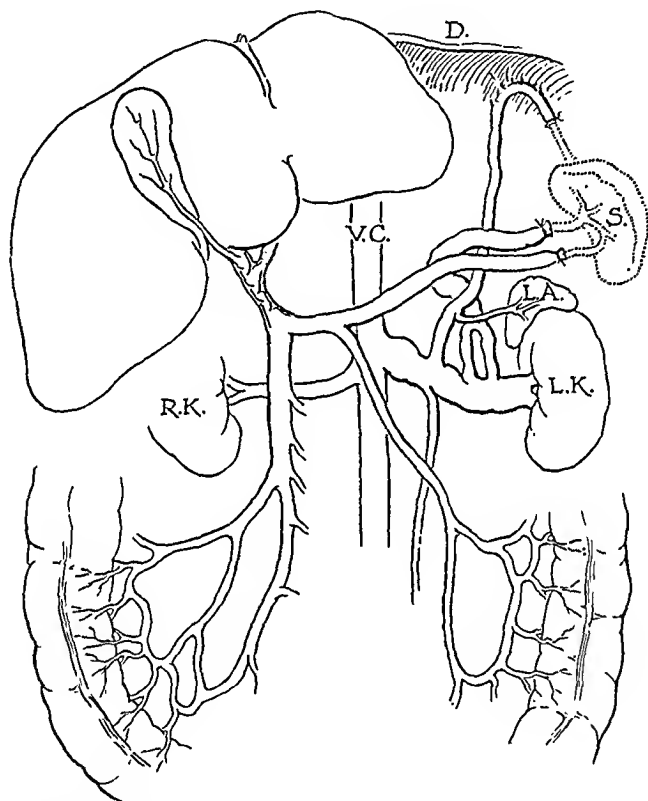


Fig. 1.—Diagram of the collateral circulation. The spleen (S) and the adjacent portions of the veins removed at operation are indicated by dotted lines. L. K. indicates left kidney; R. K., right kidney; V. C., vena cava inferior, and L. A., left adrenal gland.

*Summary of the Case.*—An obese white woman, 34 years of age, suffered from epigastric pain and repeated gastric hemorrhages at intervals of three or four months for a period of two years. The spleen was palpable. These hemorrhages had not induced anemia, for the erythrocyte count one month after the last hemorrhage was 4,900,000. The platelet count ranged from 86,000 to 104,000 before splenectomy to 190,000 three days afterward. The leukocyte count was 7,500 before operation. Jaundice and ascites were significantly absent. The clinical diagnosis was thrombocytopenic purpura, splenomegaly and gallstones.

The spleen, after the escape of much blood, weighed 397 Gm. and showed diffuse fibrosis of the pulp but not the fibro-adenia of Banti's disease.

Autopsy revealed obliteration, canalization and partial calcification of the greater part of the main stem of the portal vein. At the hilus this condition gave place to a cavernous transformation or replacement of the vein which extended for a short distance into the liver. No satisfactory explanation of the repeated gastric hemorrhages was found. Varices were not present in the lower end of the esophagus, the usual



Fig. 2.—Transverse section ( $\times 7.5$ ) through the portal vein at the upper border of the pancreas. One of the channels in the old vein has been opened longitudinally, and the sectioned edges of the wall are seen at the upper center. A calcified mass is attached to the inner surface of the old wall. Lymph nodes are seen at the left. Numerous small venous channels are visible in the old wall of the portal vein (enlarged vasa vasorum) and in the mass of fibrous tissue in the upper right corner.

source of hemorrhage in such cases. The collateral circulation, which was so adequate that ascites never developed, was by way of huge varicose venous connections between the splenic and the left renal vein. This exceedingly rare and unsuspected collateral circulation defeated the favorable results to be expected from splenectomy. Removal of the



Fig. 3.—Section ( $\times 10.5$ ) just inside the hilus of the liver, showing numerous venous channels and several arteries. Several nerves, cut transversely, traverse the mass. A little above and to the right of the center is an area of necrosis with lymphocytic infiltration. In the lower left portion of the field are many proliferated bile ducts. The liver is not fibrotic.

spleen and ligation of the splenic vein blocked the only open channel through which blood from the stomach and the intestinal tract could return to the general circulation.

#### THROMBOSIS OF THE PORTAL VEIN

Acute thrombosis of the portal vein is not uncommon. Lissauer reported 68 cases of portal thrombosis among 26,687 autopsies, and



Fig. 4.—Section ( $\times 7.5$ ) of a nearly normal triad located more deeply in the liver. There is no fibrosis of the liver.

Webster, 21 cases among 6,050 autopsies. The largest absolute number of cases in each report were associated with cirrhosis of the liver. The highest percentage of cases of portal thrombosis were associated

with swelling of the periportal lymph glands (46 per cent), abscess of the spleen (28 per cent), carcinoma of the pancreas (24 per cent) and primary carcinoma of the liver (11 per cent) in Lissauer's series and with cholangitis (10.5 per cent) in Webster's series. Acute complete thrombosis of the portal vein usually progresses rapidly to a fatal termination from infarction of the small intestine, as pointed out by Josselin de Jong and others.

Chronic occlusion of the portal vein, on the other hand, runs a much longer course, up to twenty years or more (Wohlwill, case 1; Gruber, case 4; Risel, case 1; H. Gross, case 1; Pick; Hart, and Umber). The changes in the portal vein range from transformation into an impervious fibrous cord (Pippow) often with calcification, to replacement by an angiomatous or cavernous mass "the size of a goose egg" (Pick).

TABLE 1.—*Distribution of Patients by Age and Sex*

Age, Years	Group 1			Group 2			Grand Total
	Males	Females	Total	Males	Females	Total	
0-19.....	0	2	2	0	0	0	2
20-29.....	6	2	8	4	2	6	14
30-39.....	8	1	9	5	5	10	19
40-49.....	5	3	8	7	3	10	18
50-59.....	7	2	9	5	4	9	18
60-69.....	3	3	6	1	0	1	7
Not stated.....	(2)	(1)	13	0	0	4	17
Totals.....	31	14	55	22	14	40	95

This report is based on a study of the case here reported and the reports of 94 cases collected from the literature. Since some of the recorded case reports are too meager to be of much value, this fact is taken into account in analyzing the data. These cases may be divided into two groups: (1) those in which the portal vein was replaced by fibrous tissue with little or no canalization and (2) those in which the portal vein and/or its immediate vicinity was transformed into a cavernous mass of tortuous blood channels. This classification is significant because (1) the type of change has an effect on the clinical picture, (2) it influences the establishment of a collateral circulation and (3) it is a factor in determining the cause of death.

From table 1 it appears that chronic occlusion of the portal vein is about twice as frequent in men as in women. In all the cases included in this table autopsy was performed, but it was not possible to make corrections for the differences in the relative number of males and females in the total series of autopsies.

The most frequent symptoms and physical signs recorded were ascites, abdominal pain, hematemesis and a palpable spleen. The relative frequency of these symptoms and the causes of death are shown in table 2.

From table 2 several significant facts appear. Abdominal pain, usually located in the epigastrium but varying in intensity, duration and quality, was the most frequent symptom in each group. Ascites was much more frequently present in group 1. The same is essentially true of hematemesis. Loss of weight was present in from one fourth to one half of the patients in each group. Jaundice, usually slight, was observed with sufficient frequency to give it some diagnostic importance. The spleen was specifically stated to be palpable during life in a high percentage of cases; it was observed at autopsy to be sufficiently large to have been palpable in an even higher percentage. The most frequent cause of death in group 1 was gastric hemorrhage; in group 2, infarction of the intestines. The reason for the difference in distribution of ascites and hematemesis and the differences in the causes of death will be discussed later.

In 27 cases in group 1 no clinical diagnosis was given. Among the remaining 28 cases of this group, a correct diagnosis of thrombosis of the portal vein was given in 5 cases (Gruber, case 3; Kaspar, case 4; Hecht; Oppolzer, and Bruzelius and Key); a diagnosis of thrombosis of the portal vein or some other disease, in 4 cases (Achard; Leyden;

TABLE 2.—Data on the Symptoms and the Causes of Death

	Group 1					Group 2				
	Pres- ent	Ab- sent	Per- centage*	Not Stated	Total	Pres- ent	Ab- sent	Per- centage*	Not Stated	Total
Symptoms										
Ascites.....	40	7	85; 75	7	54	15	16	48; 37	9	40
Hematemesis.....	26	6	81; 47	23	55	23	8	74; 57	9	40
Abdominal pain...	29	0	100; 53	25	54	27	2	93; 67	11	40
Icterus.....	11	12	48; 20	32	55	8	13	38; 20	19	40
Loss of weight....	14	7	67; 26	34	55	13	7	65; 22	20	40
Spleen palpable...	25	3	89; 45	27	55	14	1	93; 35	25	40
Spleen very large (post mortem)...	32					23				
Spleen normal or small.....	6	..	84; 70	8	46	1	..	96; 77	7	36
Cause of death										
Hemorrhage.....	22	..	49	..	45	12	..	30	..	36
Intestinal infarct.	9	..	20	..		16	..	44	..	
Other causes.....	15	..	33	..		8	..	26	..	
Unstated cause....	..	..	..	..	10	..	..	..	..	4

\* When two figures are given in this column the first is the percentage of cases in which the condition was present among the cases in which it was specifically mentioned; the second figure is the percentage of cases in which the condition was present among the total number of cases in the group.

Botkin, and Fleischhauer, case 2). Mention was made of ulcer of the stomach or duodenum in 7 cases, of cirrhosis of the liver in 6 cases, of Banti's disease in 4 cases and of pernicious anemia in 2 cases. In 10 cases in group 2 the clinical diagnosis was not mentioned. In this group the diagnosis was correct in only 4 cases (Gruber, case 4; Eppinger, case 32; Lommel, and Martin and Klages, case 3). The more common clinical diagnoses were ulcer of the stomach and Banti's disease (in 5 cases) and cirrhosis of the liver (in 4 cases). Other diagnoses included

such nonrelated conditions as syphilitic aortitis and dissecting aneurysm, myelogenous leukemia, sarcoma and tuberculosis of the spleen and thrombocytopenic purpura and gallstones. In 2 cases of fatal tuberculosis of the lungs (Loeb and Ehrentheil, case 3) the lesion of the portal vein characteristic of group 2 was an incidental observation at autopsy without symptoms referable to the condition during life. Kaspar stated that in only about 12 per cent of the cases of chronic thrombosis of the portal vein was a correct diagnosis made clinically.

#### ETIOLOGY OF THROMBOSIS OF THE PORTAL VEIN

Alterations in the composition of the blood, slowing of the blood flow and injury to the lining of the vessel have been accepted as the fundamental factors in the causation of thrombosis in general ever since the pioneer but thorough work of Cohnheim and of Welch. These factors play a part in thrombosis of the portal vein in several ways.

1. *Alterations in the Composition of the Blood.*—Polycythemia was present in at least 4 cases in this series. Kratzeisen, Gruber, Lommel, Versé and Emmerich each considered this a factor in his case. The erythrocyte count in Kratzeisen's case (also described by Gruber) was up to 6,500,000; in Lommel's case, as high as 10,000,000. Versé and Kratzeisen stated definitely that hematemeses did not occur in their patients; neither Emmerich nor Lommel mentioned hematemeses in the clinical histories. In the case here reported the red blood cell count was 4,900,000 one month after the last gastric hemorrhage. Kratzeisen and Gruber said they believed that the increased viscosity of the blood associated with polycythemia may well be a factor in thrombosis.

Marked thrombocythemia was present in the cases reported by Block and Klemperer. Rosenthal reported on thrombocythemia when the spleen was removed seven years before death in the case later reported on by Klemperer. At the time of operation the highest platelet count was 1,780,000. Rosenthal differentiated two types of Banti's disease: 1. In the thrombocytopenic type the platelet count is normal or reduced but rises temporarily immediately after splenectomy, with a quick return to normal. In cases of this type splenectomy gives favorable results. 2. In the thrombocythemic form of the disease splenectomy is followed by a long continued rise in the platelet count to as high as 1,000,000 per cubic millimeter, with a corresponding increase in the danger from thrombosis. Bryce also discussed this possible etiologic factor and reported on 2 cases of thrombosis of the splenic and portal veins, in one of which the platelet count after splenectomy was above normal (up to 700,000); in the other case thrombocytopenia was more marked than in the case here reported. Bryce emphasized the fact that in many cases enlargement of the spleen is associated with a low platelet

count and that after splenectomy in these cases the platelets often increase in number. He stated the conclusion that while thrombocythemia may not always be associated with thrombosis, it is an excellent criterion to use in determining the surgical risk of splenectomy.

2. *Alterations in Blood Flow.*—Changes in the blood flow as a result of intrahepatic obstruction constitute an important factor in the high incidence of thrombosis of the portal vein in atrophic cirrhosis of the liver. A further factor is the thickening of the wall of the vein, which, as pointed out by Weeber, is an almost constant accompaniment of cirrhosis and is probably due to the increased pressure in the portal vein. Thrombosis of the portal vein does not appear to be frequent in passive hyperemia of the liver and splanchnic region resulting from diseases of the heart. In the large series of cases of venous thrombosis associated with myocardial failure analyzed by Welch and by Sladen and Winternitz there was no case of thrombosis of the portal vein. Interference with the blood flow in the portal vein as a result of mechanical pressure by enlarged lymph glands and carcinoma of the head of the pancreas is a potent factor in thrombosis of this vein. In Lissauer's series 46 per cent of the patients with markedly enlarged periportal lymph glands also had thrombosis of the portal vein. Edens even stated that he considered that pressure on the portal vein by a distended stomach while the patient is lying on his back, as in taking an early afternoon nap, may cause sufficient circulatory interference to be a factor in the causation of thrombosis of the portal vein.

3. *Primary Changes in the Wall of the Portal Vein Capable of Inducing Thrombosis.*—These changes assume several forms. Phlebosclerosis, having many characteristics in common with atherosclerosis of arteries, is not infrequently observed as a primary disease of the vessel. The process begins in the intima and may progress to a stage in which there is extensive calcification. This condition was long ago cited as a factor in the etiology of thrombosis of the portal vein by Spiegelberg, Borrmann and Welch. Saxer, on the other hand, insisted that the phlebosclerosis is the result and not the cause of the thrombosis, because he had never observed the condition except in thrombosed veins. Later Buday, Hart, Winkler, Gruber and others showed that primary sclerosis of the portal vein does occur.

Phlebosclerosis is a degenerative process. Inflammation of the wall of the portal vein is usually secondary. That primary phlebitis or pylephlebitis of the portal vein also occurs has been pointed out by Lewis and Rosenow. Omphalogenic phlebitis in infancy was thought to have been a possible factor in case 4 reported by Gruber.

Pfifferling and Klemm were among the earliest authors to consider syphilis of the portal vein an important etiologic factor in throm-



bosis of this vein. Later M. Simmonds reported a larger series of cases and presented stronger evidence on the relation of thrombosis of the portal vein to syphilis of the wall of this vessel. The syphilitic lesion of the vein may be degenerative and affect the media, or it may be exudative and involve the other coats of the vein. It may be present alone or associated with typical gummas or syphilitic scars in the liver (Hart, Jastrowitz, Bülow, Loewenfeld and Borrmann). Simmonds' views have been accepted and confirmed by Ghon, Zinn, Wohlwill, Chiari, H. Gross and Falkenberg.

4. *Secondary Changes in the Portal Vein That May Influence Thrombosis.*—These changes are numerous and are chiefly the result of infection, but trauma is apparently a causative agent in some cases. This view was especially advocated by Heller, Schmorl, Ponfick, Borrmann, Köbrich, Wilke, A. Gross and Hecht. The patient reported on by Heller and Gross jumped from a height of 0.75 meter into a boat. Within ten minutes he became dizzy and fainted, and he afterward suffered from hematemesis and melena for several days. Death occurred after two years, from gastric hemorrhage, and at autopsy the portal vein was observed to be occluded by an old, completely organized and canalized thrombus. Other cases in which the condition was believed to have followed trauma were based on similar evidence of the *post hoc ergo propter hoc* variety. However, Heller, Köbrich and Wilke said that they believed that the presence of microscopic splitting of the elastic coat of the vein is confirmatory evidence of trauma.

Infections and other pathologic processes in the gastro-intestinal tract and spleen and abscess of the liver have been found associated with thrombosis of the portal vein. The frequency with which appendicitis leads to thrombosis of the portal vein has been emphasized by Fleischhauer, Ehrentheil, Lissner and Kuhr, each of whom has reported a case in which this etiology was probable. Otschkin said that he believed that in about 1 per cent of cases advanced appendicitis results in thrombosis of the portal vein. In his 1,692 cases of appendicitis there were 15 (0.9 per cent), and in 8,667 case reports collected by him there were 58 (0.67 per cent) cases in which appendicitis was associated with thrombosis of the portal vein.

Various acute infections have been held responsible for the thrombosis or, in the absence of any other obvious cause, have been considered as a possible or probable factor in specific cases: scarlet fever (Risel and Palmedo), pneumonia (Alexander), typhoid (H. Gross and Dock and Warthin, case 1), endocarditis (Goldmann), infection of the neck (Kratzeisen) and infection of the scrotum (Gruber). Even malaria has been mentioned as an antecedent disease (Ehrentheil).

Puerperal and other infections of the female genital tract have with greater reason been held to be etiologic factors in thrombosis of the portal vein by Rommelaere, Schulz and Müller, Block and others. Bucura collected reports of 12 cases from the literature and added 1 of his own in which thrombosis of the portal and/or the mesenteric vein occurred during pregnancy or the puerperium. Linzenmeier said he did not consider the portal system as a closed system and that thrombosis may extend directly, i. e., by continuity, from the veins of the uterus to branches of the portal vein. In my case the patient had an abortion and an operation for a "pus tube" eight years prior to death and six years before the onset of symptoms. Hysterectomy and salpingectomy were performed four years before death and two years before the appearance of the terminal clinical manifestations.

5. *Extension of an Inflammatory or Neoplastic Process from Surrounding Structures to the Portal Vein.*—This is an undoubted factor in many cases, e. g., enlarged periportal lymph glands (Lissauer), carcinoma of the pancreas (Kaspar), gallstone impacted in the common duct (Wurm), cholecystitis and choledochitis (Wurm, Alexander, Dock and Warthin, Wohlwill and Edens), chronic gastric and duodenal ulcers (Kaspar and A. Gross), pancreatitis and fat necrosis (Martin and Klages, Klages, Steinhaus and Edens), stone in the pancreatic duct (Chiari), chronic peritonitis with perivenous inflammation (Achard, Walker, Gohrbandt and Wohlwill) and foreign bodies and parasites (Wohlwill—a "worm" was removed from his patient's liver).

6. *Thrombosis of the Portal Vein Without Determinable Cause.*—The so-called marantic thrombi are instances of this type.

#### NATURE OF THE LESION IN THE PORTAL VEIN

The cases of chronic occlusion of the portal vein may be divided into two groups. In the cases in group 1 the vein was reduced to a fibrous cord with relatively slight canalization. In Pippow's case only did there appear to have been complete obliteration of the lumen of the vessel. In all the others the lumen was markedly narrowed and was frequently associated with one or a few narrow tortuous channels in the thickened wall. There is little if any question but that the condition in these cases was the result of organization and canalization of a mural or incompletely obturating thrombus of the portal vein. The extent of the lesion along the vein and its branches was determined solely by the extent of the original thrombus.

In the cases in group 2 the portal vein had been replaced by an elongated mass of spongy, cavernous tissue in which traces of the wall of the vein were usually, but not always (Pick, Hart and Meyer), discernable. This alteration occurred at any place between the junction

of the splenic and the mesenteric vein and the hilus or even extended deeply into the liver. In some cases this change was present also in the splenic vein. Concerning the nature of this lesion, there has been much dispute, and four views have been presented on the mechanism of its production, as follows:

1. The majority of those who have studied this condition have stated the belief that it is merely the result of organization of a thrombus with marked recanalization.

2. Versé, Risel, Emmerich and Josselin de Jong stated that in their opinion organization and recanalization of a thrombus in the portal vein are accompanied with a compensatory dilatation of the accessory portal veins of Sappey and the growth of telangiectatic granulation tissue in the hepatoduodenal ligament. It is therefore in the nature of an acquired anatomic anomaly.

3. Beitzke, Hart, Fleischhauer, Meyer, H. Gross and Benda stated that they considered the lesion a congenital malformation. Fleischhauer reproduced an illustration from Keibel and Mall's textbook of embryology to show the possibility of the development of such an anomaly by the atypical development of the plexus of veins between the omphalo-mesenteric and the hepatic vein during the second month of fetal life. He apparently considered that this plexus extended beyond the liver and met the portal vein at about the level of the head of the pancreas.

4. Pick argued strongly for the view that the condition is a neoplasm—an angioma or cavernoma of the hepatoduodenal ligament.

The difference in the extent of the cavernous transformation of the portal vein in different cases is one of the chief sources of disagreement as to the nature of the lesion. In the more marked cases the change patently exceeded that ordinarily seen in canalization of a thrombus, for it sometimes extended laterally far beyond the original limits of the vein itself. In Pick's case the cavernous mass was said to be "the size of a goose egg;" in Wohlwill's first case, the "size of a child's fist;" in Fleischhauer's case 2, "three fingers thick," and in Martin and Klages' first case, 10 by 15 mm. in diameter. The mass sometimes involved the entire portal vein from its origin at the confluence of the splenic and the mesenteric vein to its division into its branches at the hilus of the liver, as in the cases of Pick, Emmerich, Gruber (cases 2 and 4) and Ehrentheil (cases 1 and 2). The change was occasionally limited to the region of the hilus of the liver, as in the cases of Devé, Wohlwill (case 1) and Ehrentheil (case 5). It sometimes involved only a part of the vein—above the pancreas, as in Fleischhauer's case 2 and Gruber's case 1, or it was limited to the region of the pancreas, as in Falkenberg's case. In the majority of cases the cavernous tissue extended along the branches of the portal vein into the liver. In most instances this

extension was slight, up to 1 or 2 cm.; in a few cases, as in Ehrentheil's case 2, the change in the portal vein extended deeply into the liver. In the cases reported by Versé and Emmerich and in Ehrentheil's case 3 the cavernous change was present also in the splenic vein; in Gruber's case 3, about the mesenteric veins, and in Kuhr's case 2, in the pancreas. In 1 of the 2 cases in which the cavernous mass was largest the spongy mass invaded the liver only slightly, (Wohlwill's case 1), and in the other case (Pick) the change apparently stopped at the hilus.

In most of the cases in this group traces of the portal vein were still recognizable, at least by means of stains for elastic tissue, but no traces of the portal vein were recognizable in the cases reported by Pick, Beitzke, Hart, Meyer, Hulk, Cabred, Gruber (case 4), Josselin de Jong (case 8) and Martin and Klages (case 1). This fact was given great weight by Pick in his argument in favor of the neoplastic nature of the lesion.

In 18 cases nerves and lymph glands were observed within the cavernous tissue. Bile ducts also were present in the mass in the cases reported by Risel, Versé, Josselin de Jong (case 8) and Ehrentheil (case 5). The cavernous tissue extended into the pancreas in the cases of Versé and Ehrentheil (case 3).

Pick's reasons for believing that the lesion is a true neoplasm were as follows: 1. The mass was too large to be the result of organization and canalization of a thrombus; but the formation of telangiectatic granulation tissue, as suggested by Versé, might well have accounted for the massiveness of the lesion. This view was strengthened by the definite evidence of inflammatory changes about the portal vein in Gruber's case 2 and in Ehrentheil's cases 1, 2 and 4. 2. Pick stated that he considered the absence of any remnant of the portal vein as evidence of the neoplastic nature of the lesion, while Beitzke and others said they considered the lesion to be a congenital anomaly. Kuhr, however, insisted that as a result of chronic inflammation the wall of the vein could have been replaced by scar tissue. 3. The presence of nerves, bile ducts and lymph glands within the cavernous mass convinced Pick that the lesion was a tumor; it convinced Beitzke that it was a congenital anomaly and convinced Versé, Risel and others that it was an acquired anomaly. 4. Pick called attention to the fact that since cavernous hemangioma is known to occur outside the liver there is no reason that such a tumor might not be present in the hepatoduodenal ligament.

Perhaps the simplest explanation of the lesion is that its etiology varies in different cases. No one of the four theories just mentioned is satisfactory in all cases or explains all the clinical manifestations and pathologic features. If it is a tumor, it is difficult to explain the extension into the liver in so many cases and the limitation of the change to the

media of the vein in Falkenberg's case. Falkenberg suggested that if it is neoplastic it must be of the nature of a hamartoma or a choristoma. Kaspar and Falkenberg mentioned the difficulty of explaining the first appearance of symptoms late in life if the condition is congenital. Pick's case comes nearer to complying with the criteria of tumor than any other of the reported cases. Perhaps it will be necessary to accept his opinion, in spite of the doubts concerning it expressed by Kaufmann and many others.

#### COLLATERAL CIRCULATION

Pick has made a useful distinction between two types of collateral circulation in cases of obstruction in the portal area—the hepatopetal and the hepatofugal. When the circulation through the liver itself is unimpeded and the obstruction is limited to the portal vein, the hepatopetal circulation may compensate more or less completely by shunting the blood around the obstruction. This hepatopetal circulation is accomplished through numerous normal or anomalous channels which enlarge to accommodate the increased flow through them. In 8 of his 160 dissections (5 per cent) Walcker was able to demonstrate collateral veins, not *vasa vasorum*, accompanying the portal vein. More numerous and constant are the accessory portal veins of Sappey, which consist of "small vessels which arise in the folds of the peritoneum connected with the liver or which come from the stomach and pass either into the stem of the portal vein or directly into the substance of the liver." Specifically, they consist of (1) the deep cystic veins, from 15 to 20 in number; (2) the epiploic veins of the lesser omentum and the hepatocolic and hepatorenal ligaments; (3) veins of the hilus of the liver, the *vasa vasorum* of the portal vein and hepatic artery, and the veins in the wall of the common duct; (4) diaphragmatic veins; (5) veins in the suspensory ligament of the liver, and (6) the para-umbilical veins. Finally, the channels in the cavernous mass and in the canalized thrombus transmit blood to the liver from the abdominal viscera.

In portal cirrhosis of the liver the hepatofugal circulation shunts much of the blood from the abdominal viscera around the intrahepatic hindrance. McIndoe has classified the various parts of the hepatofugal collateral circulation into three groups on an embryologic basis: 1. The veins of group A are located at the two places in the gastro-intestinal tract where absorbing epithelium comes into contact with protective epithelium, i. e., at the cardia and at the anus. The veins at the cardia furnish an outlet to the superior vena cava and are best seen in esophageal varices. The veins at the anus provide an outlet to the inferior vena cava by way of the hemorrhoidal veins. 2. The veins of group B occur at the site of the obliterated fetal circulation—the para-umbilical veins in the falciform ligament of the liver. 3. The veins of group C

are found at all situations within the abdomen where the gastro-intestinal tract, its appendages or the glands developed from it become retro-peritoneal developmentally or adherent to the abdominal walls as a result of some pathologic process.

Of the 55 cases included in group 1 in table 1, no statement was made concerning the collateral circulation in 15, and in 8 others the complete original article was not accessible. In the remaining cases there were 25 cases of esophageal varices, 1 case of esophageal and hemorrhoidal varices, 3 cases of hemorrhoidal varices and 1 case of varix in the stomach near the pylorus. In 2 cases (Schulz and Müller and Alexander) no collateral vessels were noted. In other words, the collateral circulation in 94 per cent of these cases belonged wholly or in part to McIndoe's group A. In 5 cases (17 per cent) collateral vessels passed also to the umbilicus and the veins of the anterior portion of the abdominal wall; these cases fall in McIndoe's group B. In 10 cases (32 per cent) there was additional collateral circulation that belonged to McIndoe's group C.

Among the 40 cases in my group 2, the collateral circulation was not described in 4, and the complete data were not accessible in 4. Only 17 of the remaining 32 patients had esophageal varices, and one had both esophageal and hemorrhoidal varices, and in 5 cases it was specifically stated that no esophageal varices were present. In contrast to the first group, only 56.3 per cent of the patients in group 2 had a collateral circulation of the type of McIndoe's group A, 3 (9.4 per cent) belonged in McIndoe's group B and 24 (75 per cent) in group C. This last figure is inaccurate in that it does not take into account the circulation through the cavernous mass itself, and this is an important part of the hepatopetal circulation in these cases. In Ehrentheil's cases 2 and 3 the cavernous tissue was the only detectable collateral circulation, and there was no ascites in either case. In 15 cases (47 per cent) an additional hepatopetal collateral circulation was specifically mentioned by references, for instance, to dilated veins of Sappey, adhesions between the stomach or duodenum and the liver or gallbladder.

When esophageal varices form an important part of the collateral circulation, they usually drain by way of the diaphragmatic, internal mammary, azygos and hemiazygos veins into the superior vena cava. It is extremely rare in a case of intrahepatic or extrahepatic obstruction of the portal veins to observe blood from the stomach and spleen reaching the inferior vena cava as in the present case. In a few cases (Fleischhauer, case 2; Klemperer, and Versé) there was drainage by way of adhesions in the left upper quadrant of the abdomen into the left renal or adrenal vein. In Lossen's case the celiac veins were markedly varicose and "extended downward and to the left about the left

kidney." The termination of these varicose veins was not clearly described. In Curschmann's case there was a communicating vein "as large as the little finger" between the coronary veins of the stomach and the left suprarenal vein.

I have been able to find in the literature reports of only 6 cases in which the collateral circulation was similar to that in the case here reported:

1. Tuffier. There was a communication between the splenic and the left renal vein.

2. Lejars. A large vein the size of a finger came off from the left renal vein and was connected by one branch with the plexus of the inferior veins of the diaphragm and by another larger branch which was lost in a postpancreatic plexus of veins which "communicated abundantly" with the splenic vein.

3. Mariau. There was a communication behind the pancreas between the splenic and the left renal vein.

4. Saxer. A huge varix in the wall of the stomach communicated with the splenic vein, and this, in turn, communicated with the left adrenal vein.

5. Pensa. There was an anastomosis between the splenic vein and the left renal vein.

6. H. Gross. The dilated splenic vein was continued by way of a wide channel through the substance of the spleen to its upper pole and thence by large varicose veins along the diaphragm to the left adrenal vein.

These 7 cases (6 previously reported) indicate the extreme rarity of this type of anastomosis. Gross, however, insisted that there is normally a communication between the splenic vein and the left renal vein by way of the left phrenic vein, which anastomoses with the veins of the diaphragm and these with veins in the capsule of the spleen. If this is true, it is evident from the infrequency of their being sufficiently large for detection that they do not often form a part of the hepatofugal circulation in cases of portal obstruction and cirrhosis of the liver. This is fortunate, as otherwise splenectomy would entail a prohibitive surgical risk.

#### CHANGES IN OTHER ORGANS

The most constant accompaniment of chronic occlusion or stenosis of the portal vein is enlargement of the spleen. The relative frequency of splenomegaly in the two groups is shown in table 2. The weight of the spleen was given in 29 cases, and the dimensions in centimeters, in 19 cases; in the remainder, information concerning the size of the spleen was entirely lacking or was stated only in general terms. In 3

(21 per cent) of the 14 cases in group 1 the spleen weighed more than 1,000 Gm., while in 6 (40 per cent) of the 15 cases in group 2 its weight exceeded 1,000 Gm. The largest spleen in group 1 weighed 2,150 Gm. (Mennet's case 1); the largest in group 2, 2,000 Gm. (Emmerich). The most frequent change in the spleen was fibrosis, in most cases diffuse and confined to the pulp. In a few cases it showed the fibro-adenia characteristic of Banti's disease. Chronic perisplenitis, ancient and recent infarcts, sclerosis and thrombosis of the splenic vein were frequently recorded.

Changes in the liver are not as extensive or as frequent as might be supposed. The weight of this organ was given in only 28 cases (12 in group 1 and 16 in group 2). One half or more of the livers in these cases weighed less than 1,500 Gm. Boyd has shown that the median weight of the liver of men between the ages of 25 and 55 ranged

TABLE 3.—*Data on the Weight of the Liver*

Weight of Liver, Gm.	Group 1		Group 2	
	Number of Cases	Percentage	Number of Cases	Percentage
750-999.....	2	16.6	1	6.2
1,000-1,249.....	4	33.3	2	12.5
1,250-1,499.....	3	25.0	5	31.3
1,500-1,749.....	1	8.3	7	43.7
1,750-1,999.....	1	8.3	0	0.0
2,000-2,249.....	0	0.0	1	6.2
2,250-2,500.....	1	8.3	0	0.0
Totals.....	12	99.8	16	99.9

from 1,820 to 1,840 Gm., while the median weight of women aged between 20 and 60 fluctuated between 1,460 and 1,430 Gm. The weights in the 28 cases in the two groups in this series are shown in table 3. In approximately 75 per cent of the cases in group 1 the liver weighed less than 1,500 Gm., and in 50 per cent of the cases in group 2 it weighed less than 1,500 Gm. It appears probable, therefore, that the hepatopetal circulation through the cavernous tissue at the site of the portal vein in the cases in group 2 was a factor in maintaining the nutrition of the liver. In the greatest number of cases the reduction in the size of the liver was apparently due to simple atrophy (Saxer, Pick, Buday and Kretz); in a smaller number there was moderate fibrosis, usually associated with an extension of the lesion in the portal vein into the liver; in only 7 cases in group 1 and in none in group 2 was there actual evidence of cirrhosis. In 11 of the 24 cases in group 2 in which the hepatic artery was mentioned it was specifically described as dilated. Such a change in this artery was mentioned in only 1 case in group 1. Several authors said that they considered the dilatation of the hepatic



artery as a compensatory process. If it is, then the rarity of this arterial change in group 1, in which the flow through the portal vein was interfered with as much as or more than in group 2, is difficult to understand.

Definite syphilis of the liver with gummas and marked scarring was present in the cases of Hart, Jastrowitz, Bülow Löwenfeld and Borrmann. Chronic adhesive perihepatitis was frequently observed. Proliferation of the bile ducts was recorded by Risel and Chiari and in the description of my case (fig. 3). Infarcts of the liver were mentioned by Lommel, Ehrentheil (case 4) and Kaspar (case 3). Changes in the liver sometimes produced a marked asymmetry in the organ, such as disproportionate atrophy of one lobe (Klemperer) or hypertrophy of the caudate and/or quadrate lobes (Hecht and Martin and Klages). Gallstones, the possible relation of which to the lesion in the portal vein has been mentioned, were present in 7 cases (Alexander; Mennet, case 2; Gruber, case 4; Dock and Warthin, case 1; Hart; Falkenberg, and Emmerich).

An interesting and possibly significant observation was that of adenoma of the liver. The lesion was recorded in only 1 case in group 1 (Kaspar, case 4, and Umbreit, a doubtful case), but in 5 and possibly 6 cases (12.5 per cent) in group 2 (Risel; Kuhr, case 1; Klemperer; Meyer, and Hulk). In 1 case described by Martin and Klages (case 2) "small nodules" were present in the liver but were not further described or identified. The rather surprisingly high incidence of these adenomas has led to differences of opinion as to their origin and significance. Hulk said that they are present only incidentally; Meyer said that they, like the change in the portal vein, are malformations, while Risel and Klemperer said that they result from regenerative processes at the site of former foci of structural damage to the liver.

Acute or chronic gastric and duodenal ulcers were associated lesions in the cases reported by Bode, Kaspar, Gruber and Klemperer.

Numerous related or merely coincidental changes in the pancreas have been recorded: fat necrosis (Edens; Dock and Warthin, case 2; Wurm; Emmerich; Simmonds, and Martin and Klages, case 1), fibrosis or chronic pancreatitis (Chiari; Alexander; Falkenberg; Meyer; Wurm; Fleischhauer, and Eppinger, case 32, associated with diabetes), stone in the pancreatic duct (Chiari), thrombosis of the pancreatic veins (A. Gross, Wilke, Gruber, Köbrich, and Martin and Klages), involvement of the pancreas in the cavernous tissue about the portal vein (Falkenberg; Versé; Meyer; Gruber, case 1; Kuhr, case 2, and Ehrentheil, case 3) and ectopic pancreatic tissue, which Meyer said he thought was evidence in favor of his view that the cavernous lesion in the portal vein is a malformation.

## RELATION OF SYMPTOMS TO THE LESION

In the preceding paragraphs there have been presented (1) the chief symptoms of chronic obturation of the portal vein, (2) the nature of the two types of pathologic process encountered in this vein and (3) the pathologic changes in other organs associated with this condition. It is now possible to explain the symptoms on the basis of their underlying structural changes and to make clear the difference in distribution of symptoms and causes of death in the two groups of cases and the variable clinical picture within each group.

Epigastric pain is an almost constant, and usually the earliest, symptom. This pain is only rarely excruciating and is frequently described merely as "epigastric distress." It is irregularly intermittent; it has no definite relation to the taking of food, and it generally precedes or accompanies gastric hemorrhage, as in my case. It is logical to conclude, therefore, that the pain in this condition is on an anatomically and physiologically different basis from that of gastric and of duodenal ulcer. The pain in chronic thrombosis of the portal vein is probably related to pressure from the esophageal varicose veins, to dilatation and stretching of the veins distal to the obstruction and/or to involvement of nerves in the scar tissue or the cavernous tissue about the lesion.

Hart said he was convinced that chronic thrombosis of the portal vein is a much more frequent cause of gastric hemorrhage than is generally believed. Its apparent infrequency is due to the fact that routine examination of the portal vein is too rarely made a part of postmortem examinations. Gastric hemorrhage occurred slightly more frequently in the cases in group 1. When present it was usually the result of rupture of an esophageal varix. In Devé's case the hemorrhage was from the varix near the pylorus; in other cases, from hemorrhagic erosions or acute superficial ulcers of the stomach or duodenum (Klemperer and Simmonds). The frequency and periodicity of hematemesis was variable. Occasionally it was the first symptom and was quickly fatal, although the lesion in the portal vein discovered at autopsy was of many years' standing (Hart; Pick; Chiari; Ueber; Wurm; Kuhr, case 2, and Ehrentheil, cases 1 and 4). In the cases of Falkenberg and Lossen gastric hemorrhage occurred at the beginning of the clinical manifestation but did not recur, although these patients survived for two and twelve years, respectively, after the onset of symptoms. In other cases periods of frequent hematemesis were separated by years of freedom from this symptom. H. Gross' second patient had gastric hemorrhages forty-one and thirteen years before death; Kaspar's second patient had hemorrhages seven years before death, and A. Gross' patient, two years before death. In other cases hematemesis recurred at frequent intervals over long periods of time (in Gruber's cases 3 and 4

for eighteen and twenty-seven years, respectively; in Kuhr's case 1, for from eight to eleven years). In Loeb's case and in Ehrentheil's case 3 there were no symptoms referable to the abdomen, and the lesion of the portal vein was observed incidentally at autopsy.

In 11 cases in which hematemesis was definitely stated to have been absent (Loeb; Emmerich; Kratzeisen; Josselin de Jong; Lommel; Eppinger; Schulz and Müller; Martin and Klages, case 2; Wohlwill, case 1; Ehrentheil, case 3, and Gruber, case 2), only 2 (Gruber and Martin and Klages) were observed at autopsy to show esophageal varices. Only 1 of these 11 cases, that of Schulz and Müller, belonged in group 1. It is evident, therefore, that the hepatopetal circulation through the cavernous tissue that was characteristic in group 2 was a factor in preventing the establishment of a hepatofugal circulation through the veins at the lower end of the esophagus. Since the hepatopetal circulation is less well established in group 1, esophageal varices are more frequent in that group. This accounts for the higher mortality rate from hemorrhage in group 1 (table 2).

On the other hand, the marked tortuosity of the blood channels in the cavernous tissue characteristic of group 2 slows the blood stream and thus favors thrombosis. This, in turn, explains the higher incidence of death from infarction of the intestines in group 2.

Ascites was much more frequent in group 1 than in group 2 (table 2). The presence or absence of this symptom depends on the adequacy of the collateral circulation. Ascites occurs in three variant forms: (1) recurring over a period of years—Beitzke, seven years; Kuhr (case 1), eleven years; Mennet (case 1), seventeen years; Fleischhauer (case 1), nineteen years; (2) persistent for several years—Buday (case 2) and Gruber (case 3), each one year; Schulz and Müller, two years; Goldmann, four years; Ehrentheil (case 5), five years, and Gruber (case 4), six years, and (3) late, i. e., with the first occurrence less than one year before death. The six cases of the third form of variant were as follows:

	Total Duration of Symptoms	Ascites
Kratzeisen.....	5 to 11 years	5 or 6 weeks
Pippow.....	6 months	6 weeks
Ueber.....	20 years	2 months
Eppinger.....	7 years	5 months
Buday (case 1).....	7 months	7 months
Falkenberg.....	2 years	8 months

These variations in ascites as a symptom are related to the collateral circulation. In the recurring form the circulation periodically shows decompensation, in the persistent form it is never entirely competent and in the terminal or late form there is sudden and complete decompensation. As pointed out by Martin and Klages, rapidly developing

ascites is of grave prognostic significance. Any one or more of the other symptoms may vary with complete intermissions, a fact emphasized by Risel.

#### SPLENECTOMY IN CHRONIC OCCLUSION OF THE PORTAL VEIN

Splenectomy was performed in 5 cases in this series. The length of survival after this operation in each case was as follows: Klemperer, seven years; Kratzeisen, five months; Martin and Klages (case 1), five weeks; Simonds, three days, and Lossen, not stated. The infrequency with which the spleen is removed in this condition is surprising, for this would seem to be the logical treatment. Burton-Opitz, in careful experiments with a *Stromuhr*, determined that in the dog 21 per cent of the portal blood comes from the spleen, and W. J. Mayo has stated that splenectomy reduces by 20 per cent the amount of flow through the portal vein. This operation therefore reduces the burden on the collateral circulation by about one-fifth, probably more when the spleen is greatly enlarged. The reasons for the infrequency of splenectomy in chronic occlusion or stenosis of the portal vein are probably (1) the rarity of a correct clinical diagnosis (Kaspar), (2) the risk of serious or even fatal hemorrhage in the separation of perisplenic adhesions which are present in about 75 per cent of the cases, (3) the known danger that thrombosis of the stump of the splenic vein will extend into the portal vein and cause death from infarction of the intestine and (4) the statement of W. J. Mayo that 10 per cent of the patients with splenic anemia who survive splenectomy die within ten years from gastric hemorrhage. However, it may be remarked that patients with chronic occlusion of the portal vein survive for a period of from only a few months to two or three years once the collateral circulation has become so incompetent as to give rise to rapidly increasing ascites or the esophageal varices have become so large as to be the source of frequent copious hemorrhage.

#### SUMMARY

A case of chronic occlusion or stenosis of the portal vein is reported in which the favorable results which might have been expected from splenectomy were defeated by the presence of an unsuspected and exceedingly rare type of collateral circulation, namely, a large varicose communication between the splenic and the left renal vein.

Chronic thrombosis of the portal vein occurs in one of two forms. A mural or incompletely obturating thrombus is either organized with relatively little or no recanalization or the vein and adjacent tissue are transformed into a cavernous or angiomatous mass. There is a sharp difference of opinion as to whether the cavernous or angiomatous type is

the result of thrombosis or a malformation or is a true neoplasm. These two forms differ, relatively, in symptomatology and in the mode of death produced.

The American and English medical literature contains few references to the subject of chronic occlusion of the portal vein, although this lesion occurs with sufficient frequency to justify its consideration in the differential diagnosis of all obscure cases of gastric hemorrhage or ascites.

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# FIBROSARCOMA OF THE SOFT PARTS

WITH SPECIAL REFERENCE TO RECURRENCE AND METASTASIS

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The question of the choice of treatment for sarcoma of the soft parts is constantly recurring, with proponents of radical or conservative surgical intervention and of irradiation. In an effort to answer this question in part, the study reported on here was undertaken. Among the reports of fibrosarcoma of the soft parts in the files of the pathologic laboratories of the Huntington Memorial Hospital and the Palmer Memorial Unit of the New England Deaconess Hospital, records of one hundred and sixty-three cases were found with adequate clinical data for careful study. In many other cases sarcoma had been diagnosed, but either the follow up or the history was unsatisfactory.

The follow-up period for the living patients ranges from thirty-one years in one case to ten months for a patient operated on in 1934 and included because of the interest of the case. The great majority of patients have been followed to death or for at least three years. Three cases without follow up are included because of special features.

Seventy-two per cent of the living patients have been followed for three years or over from the onset of their disease. Of the entire group, seventy-two died, sixty from disease and others so soon after the last treatment that the probability that disease was still present was great.

The tumors represent a fair cross-section of fibrosarcoma as encountered in practice, since the cases comprised not only those of patients referred to the Huntington Memorial Hospital and the Palmer Memorial Hospital but many observed by physicians throughout the Commonwealth in their private practice and in the surgical material sent in for diagnosis to the State Tumor Diagnosis Service. One advantage of this type of material is that the tendency is toward exclusion of the cases of advanced fibrosarcoma, in many of which naturally the patient is hospitalized, especially in those institutions known for the treatment of cancer. No selection has been made of the cases other than to choose those in which an adequate history and follow up could

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From the Laboratories of Pathology of the Harvard Cancer Commission and of the New England Deaconess Hospital, and the Department of Pathology, Harvard University Medical School.

be obtained. Many physicians of Massachusetts have given time and effort to making these data available.

So often and so falsely is sarcoma said to be a disease of young persons that we present table 1, which shows a wide distribution of patients according to age. The age given is the age at the onset of symptoms. The distribution centers in the sixth decade, the mean age at the onset being 49.1 years for males and 50.4 years for females. This is about ten years younger than the average age at death from cancer of all types in Massachusetts, which is 59.3 years for males and 61.5 years for females.<sup>1</sup> Figure 1 is a graphic comparison by age groups of our patients and those in a random series of consecutive patients with carcinoma verified by autopsy. While sarcoma is more frequent in persons of the younger age groups, the distribution is not far different than that for carcinoma.

The distribution according to sex is fairly even.

TABLE 1.—*Distribution of Cases According to Age and Sex*

Age in Years*	Male	Female
0-9.....	1	1
10-19.....	2	1
20-29.....	7	6
30-39.....	11	10
40-49.....	15	19
50-59.....	12	22
60-69.....	15	13
70-79.....	9	8
80+.....	1	2
	Standard	Standard Deviation
	Deviation	of Mean
Male.....	49.1	$\pm 17.0$
Female.....	50.4	$\pm 15.4$
		$\pm 2.0$
		$\pm 1.7$

\* The age was unknown in 8 cases.

One of the difficulties in treating fibrosarcoma early is that, as in the case of other malignant tumors, pain is not an early symptom, and consequently patients do not come promptly for relief. Swelling is usually the first sign to attract the patient's attention, and in many cases in the earlier stages the condition is superficial. For some time the tumor may be freely movable, and as a rule it becomes attached to the overlying skin before it does to the underlying structures. In thirty-five of our cases the tumor was definitely intracutaneous or subcutaneous. In some instances the contour is so well defined as to give a suggestion of encapsulation, and in other instances the tumor becomes thinned and spreads diffusely into the surrounding tissue. Examination of the gross specimen usually shows a pale, fibrous, somewhat infiltrating tumor, ordinarily tending to expand the surrounding

1. Bigelow, G. H., and Lombard, H. L.: Cancer and Other Chronic Diseases in Massachusetts, Boston, Houghton Mifflin Company, 1933, p. 264.

structures, with varying degrees of vascularity. Necrosis is not nearly so marked a feature as in the case of epithelial tumors. The masses are usually resilient and are sometimes almost translucent, owing to edematous portions. Hardness, which is a marked feature of carcinoma, is frequently absent in fibrosarcoma, and when it does occur it yields to local pressure rather than offering the mass resistance of carcinoma.

So far as can be determined from the records, trauma is not an appreciable factor as an initiating agent. This is in keeping with Ewing's<sup>2</sup> findings in his recent report on the relation of tumors to trauma.

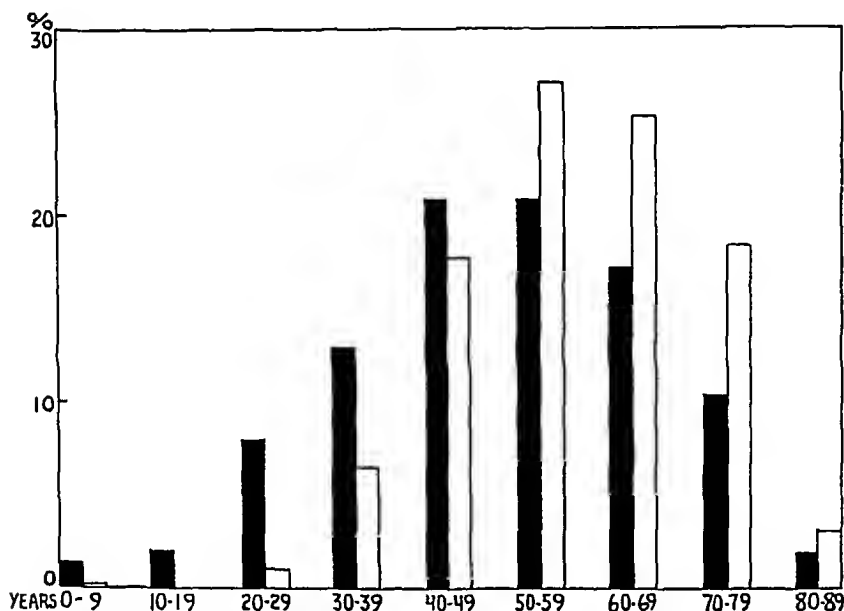


Fig. 1.—Graph showing distribution of fibrosarcoma and of carcinoma according to age. The solid black blocking indicates sarcoma; the white blocking, carcinoma.

In reviewing the older slides it is of interest to note that some of the tumors recorded as fibrosarcoma in the files were found to be atypical granulation tissue or a focus of localized fibrosis. In the cases of this type that could be followed recovery was uniformly the rule, helping to reinforce the diagnosis of a benign lesion. Sclerosing hemangioma is also a confusing lesion. It is our impression that a diagnosis of fibrosarcoma is made erroneously more frequently than true fibrosarcoma is classified as a benign lesion.

2. Ewing, J.: Modern Attitude Toward Traumatic Cancer, *Arch. Path.* **19**: 690 (May) 1935.

In most instances the tumor was treated by operation, which varied from local to radical excision; in the case of tumor of the extremities the latter was sometimes amputation. A small proportion of patients received postoperative treatment with the roentgen rays and radium, in all instances without any notable influence on the course of the disease. In several instances recurrences progressed in spite of active radiation therapy. It is of interest to note that among five cases in which the tumor was associated with definite irritative stimuli of one type or another, in two the growth followed roentgen or radium treatment of

TABLE 2.—*Types of Treatment of Fibrosarcoma*

		Operation	Operation; Roentgen Rays	Palliative	Operation; Roentgen Rays; Radium	Roentgen Rays	Radium; Roentgen Rays	Radium	Operation; Amputation; Roentgen Rays	Operation; Coley's Toxins	Radical Operation	No Treatment
Fibrosarcoma	Head.....	6	.	..	..	..	3	1	..	..	..	1
	Trunk.....	4	1	..	..	..	..	..	..	..	..	..
	Intra-abdominal region	2	2	1	..	..	..	..	..	..	..	1
	Extremities.....	17	..	..	..	..	..	1	1	1	..	..
	Special cases.....	2	..	..	..	1	..	..	..	..	..	..
Neurogenic fibrosarcoma	Head.....	7	..	..	..	..	..	..	..	..	..	..
	Trunk.....	13	2	..	..	..	..	..	..	..	..	1
	Intra-abdominal region	1	..	..	1	..	..	..	..	..	..	1
	Extremities.....	12	..	..	..	..	..	..	..	..	..	..
Fibrosarcoma with tumor giant cells	Head.....	3	1	..	..	..	1	..	..	..	..	1
	Trunk.....	6	1	..	..	..	..	..	..	..	..	..
	Intra-abdominal region	1	1	..	..	..	..	..	..	..	..	..
	Extremities.....	9	..	..	..	..	..	..	..	..	..	2
Neurogenic fibrosarcoma with tumor giant cells	Intra-abdominal region	1	..	..	..	..	..	..	..	..	..	..
	Extremities.....	8	1	..	..	..	..	..	..	..	1	..
Total.....		92	9	1	1	1	2	2	1	1	1	7

preexisting lesions. The experience at the Memorial Hospital, New York, with neurogenic tumors, reported by Stewart,<sup>3</sup> and with fibrosarcoma in general, reported by Quick and Cutler,<sup>4</sup> is not conducive to faith in radiotherapy.

The types of treatment are summarized in table 2. Operation is the most frequent method of treatment and the most successful. In this table amputation has been lumped with other operative procedures. Among the cases of sarcoma of the extremities primary amputation was carried out in four cases and preoperative roentgen radiation in two. Of the four patients, one lived ten years after treatment and died without evidence of the tumor; one is living and well after seven-tenths

3. Stewart, F. W., and Copeland, M. M.: *Am. J. Cancer* 15:1235, 1931.

4. Quick, D., and Cutler, M.: *Ann. Surg.* 86:810, 1927.



Fig. 2.—Section of fibrosarcoma of the leg, showing collagen and fibroglia fibrils, mitoses and anaplastic cells. Phosphotungstic acid-hematoxylin stain;  $\times 1,160$ .

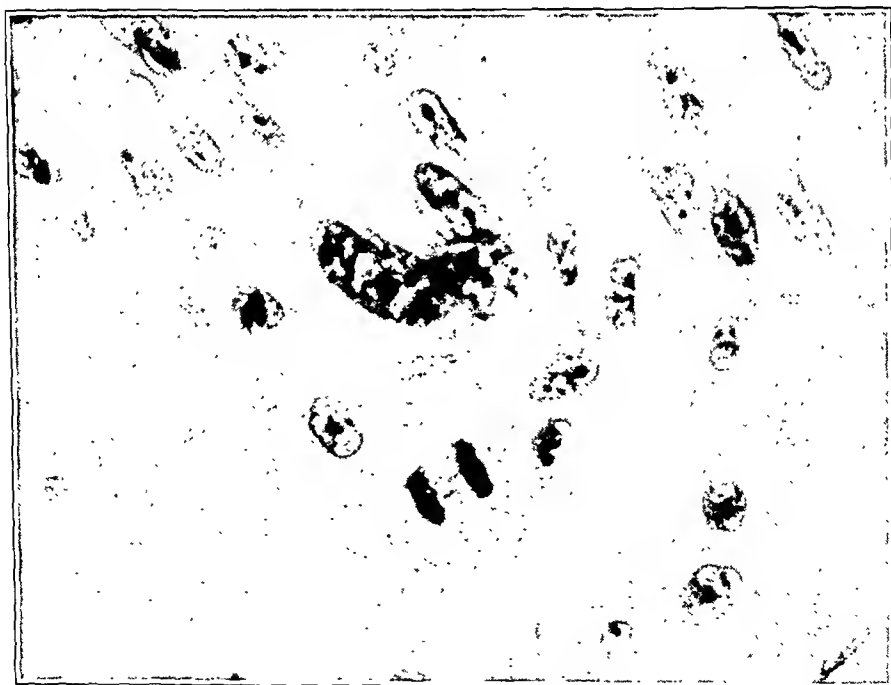


Fig. 3.—Section of fibrosarcoma of the leg, showing little intercellular substance and marked anaplasia. Phosphotungstic acid-hematoxylin stain;  $\times 1,160$ .

year, and two died with disease at the end of one year. Most of the successful operative procedures have been excision with wide margins, below as well as laterally.

Classification of the fibrosarcomas is a difficult problem and as yet unreliable. We define fibrosarcoma as a tumor of fibroblasts, forming varying amounts of collagen, which is recognized as malignant by its invasive growth, mitotic activity and at times markedly anaplastic character (figs. 2 and 3). Types of tumors ranging from benign fibroma to anaplastic sarcoma exist, and the diagnosis of the more differentiated forms is difficult. While various pathologic subdivisions have been proposed, there are only two which appeal to us as being at present definite. These are the neurogenic fibrosarcoma and a residual type classified simply as fibrosarcoma. In the case of each there are wide ranges of histologic pressure and clinical behavior.

TABLE 3.—*Location of Neurogenic Fibrosarcoma*

Head.....	8
Trunk.....	20
Intra-abdominal region.....	4
Extremities.....	31
Total.....	63

We have included as cases of neurogenic fibrosarcoma only those in which we felt that the diagnosis could be made without question. The criteria demanded for this diagnosis have been the arrangement of the cells in definite fascicles with interlacing patterning of the herring-bone type, with a tendency to somewhat wavy, elongate nuclei and with some evidence of palisading of the nuclei (figs. 4 and 5). In cases in which material was available for staining by silver the pericellular distribution of fibrils emphasized by Stout<sup>5</sup> has been of value. There is a tendency to include more cases as instances of neurogenic tumor than is warranted by a critical application of well defined characteristics. We have classified sixty-three cases in this group. The sites of the tumors were widely distributed, but in most cases the growth occurred in the extremities (table 3). In a number it occurred definitely in relation to nerves. In only two cases were the stigmas of neurofibromatosis definitely noted, although they probably existed in others. The useful papers of Stewart and Copeland<sup>3</sup> and Stout<sup>6</sup> should be consulted with regard to this group.

On the basis of our material the distinction between fibrosarcoma that is definitely neurogenic and a growth of less well defined character is largely academic. The significant difference lies between the rapidly progressing fibrosarcoma and the less actively growing tumors.

5. Stout, A. P.: *Human Cancer*, Philadelphia, Lea & Febiger, 1932.

6. Stout, A. P.: *Am. J. Cancer* 25:1, 1935.



Fig. 4.—Section of neurogenic fibrosarcoma of the leg, showing fascicle formation, elongate nuclei and collagen. Phosphotungstic acid-hematoxylin stain;  $\times 150$ .

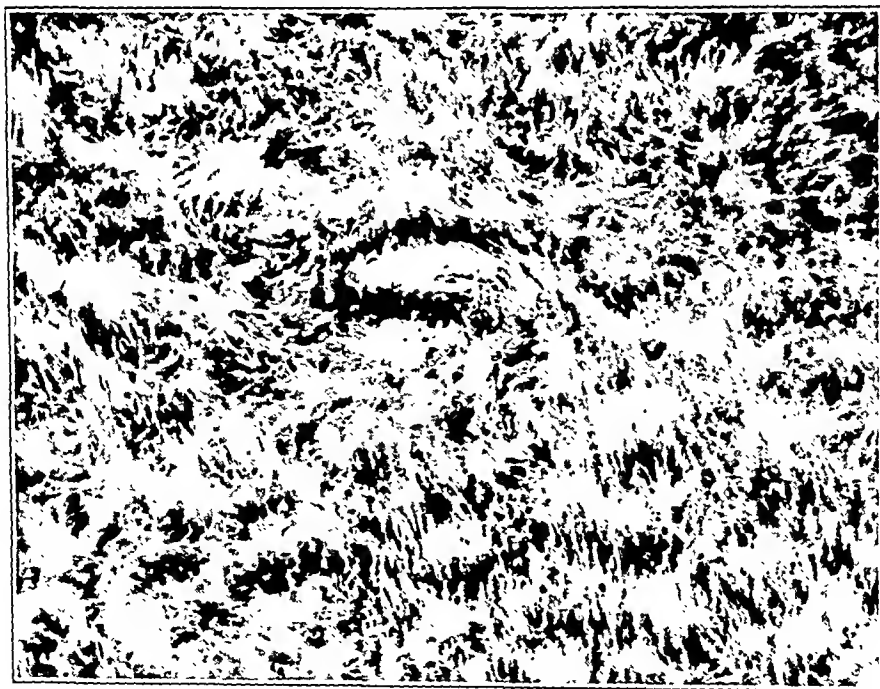


Fig. 5.—Section of neurogenic fibrosarcoma of the skin of the trunk, showing palisading of nuclei. Phosphotungstic acid-hematoxylin stain;  $\times 225$ .



In our experience the most useful histologic criterion in determining a high degree of malignancy has been the presence of a fair to a marked number of tumor giant cells. By tumor giant cells we mean large cells with two or more nuclei, variable in size and shape, or with large lobulated or bizarre nuclei, rather than unusually large tumor cells with fairly even contours of the nucleus and cytoplasm (fig. 6). Variation in the size of the cell seems to us, as to Stout, of minor significance. The number of tumor giant cells often fairly closely parallels mitotic activity.

However, the neurogenic tumor with tumor giant cells is not strikingly different in behavior from a growth without such cells. In many

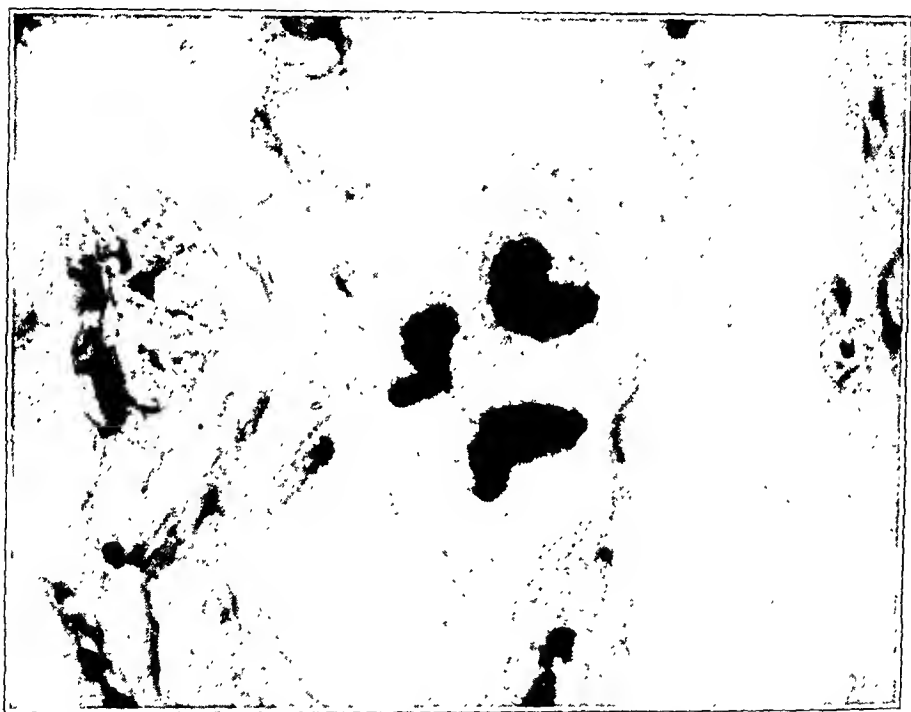


Fig. 6.—Section of fibrosarcoma of the leg, showing irregular mitosis and a tumor giant cell. Phosphotungstic acid-hematoxylin stain;  $\times 1,800$ .

of the cases, particularly in those of neurogenic fibrosarcoma, the growth has shown scattered foci of so-called myxomatous intercellular substance, and several are listed in the tables as definite instances of myxofibrosarcoma. While myxofibrosarcoma may deserve a separate classification, we prefer on the evidence so far available to regard it as a variant of fibrosarcoma, probably owing its appearance to edema of the intercellular substance (fig. 7). Our experience has paralleled that of Stout<sup>6</sup> in our failure to find mucin by specific methods of staining. Only three patients with "myxofibrosarcoma" were encountered in the group. One of these died after three and one-half years, a local operation being

followed by recurrence, which was treated by amputation of the arm, with death occurring from generalized metastases. In the second patient, a woman 45 years of age, the tumor appeared in the right small toe and did not recur after operation. The patient died without disease eight and eight-tenths years after treatment. The third patient is living and well two and five-tenths years after wide excision of a sarcoma of the left lower eyelid.

We have set aside as a separate type the well differentiated desmoid tumor of the abdominal wall, of which five cases were available for

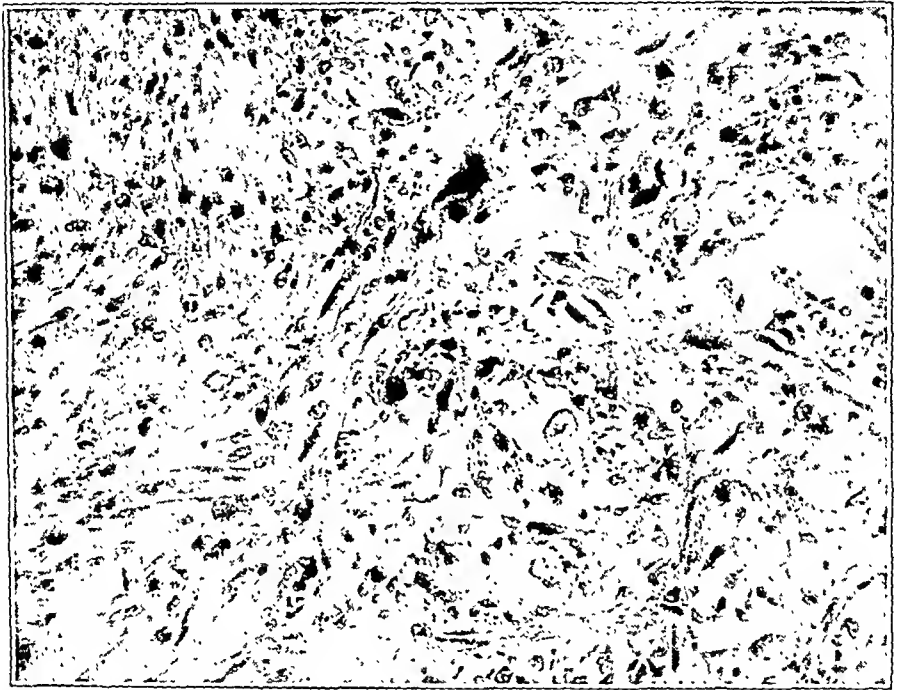


Fig. 7.—Section of fibrosarcoma, showing edema of the stroma (often called myxosarcoma). Phosphotungstic acid-hematoxylin stain;  $\times 200$ .

study, and also the fibrosarcoma of the breast, of which seventeen cases were found. In most of the latter cases the growth was definitely an adenofibrosarcoma.

In table 4 the cases in which the patient was followed for three years or over, other than those of desmoid tumor and tumor of the breast, are arranged according to histologic classification. The only significant difference here is seen in the low survival rate of the patients with fibrosarcoma with tumor giant cells.

When the average total time of survival of all the patients from the onset of disease is determined, as shown in table 5, the latter group shows a comparatively short course. This checks well with the low

survival rate for this group. Patients with neurogenic fibrosarcoma with tumor giant cells survive a definitely shorter period than those with neurogenic fibrosarcoma without tumor giant cells. The strikingly parallel behavior of fibrosarcoma of the neurogenic type and of fibrosarcoma of the non-neurogenic type is emphasized by those tables, and it suggests that the histologic distinction is without clinical significance save in cases of fibrosarcoma with tumor giant cells.

The total duration in all the cases, grouped according to the end-result, is shown in table 6.

TABLE 4.—*Classification of Fibrosarcoma with Follow Up of Three Years or Over*

	Number of Cases	Alive and Well	Percentage Alive and Well
Fibrosarcoma.....	43	15	35
Neurogenic fibrosarcoma.....	38	14	37
Fibrosarcoma with tumor giant cells.....	26	2	8
Neurogenic fibrosarcoma with tumor giant cells.....	11	4	36

TABLE 5.—*Average Total Duration from Onset to Death*

Fibrosarcoma .....	7.0 years
Neurogenic fibrosarcoma .....	7.8 years
Fibrosarcoma with tumor giant cells.....	2.2 years
Neurogenic fibrosarcoma with tumor giant cells.....	5.5 years

TABLE 6.—*Total Duration in All Cases\**

Years	Died	Living with Disease	Living and Well
Under 1.....	20	0	3
1 to 2.....	23	1	9
2 to 3.....	11	0	14
3 to 4.....	8	0	9
4 to 5.....	2	1	4
5 to 10.....	3	2	27
10 to 15.....	3	0	10
15 to 20.....	1	0	5
20 to 25.....	1	1	0
25 to 30.....	0	1	1
30 to 35.....	0	0	1
Total.....	72	6	83

\* The duration was unknown in two cases.

Since recurrence developed in over a third of the cases (sixty-four), it is obvious that local removal is often inadequate. In cases with recurrence the prognosis is grave. But eight patients who showed recurrence are living and well after three years. As a rule, if recurrence takes place it occurs within a year. Among the twenty-nine cases in which the time of recurrence was definitely known, in all but two the recurrence took place before a year had passed. The longest interval between the primary operation and recurrence was three years. Thus it can

be stated with a fair degree of probability that if in a given case a year has passed without recurrence there will be no appreciable danger subsequently.

Another feature of importance is the relation of recurrence to metastasis. Among the thirty-four cases with metastasis, in only six did this occur prior to local recurrence, and in two local recurrence was impossible because amputation had been done as the first operation. One must then recognize recurrence as having grave prognostic significance, not only with regard to the likelihood of metastasis but with regard to an ultimate fatal outcome of the disease. For this reason adequate removal at the first operation is of prime importance. In cases in which the lesion in an extremity has reached such a size that an adequate margin of healthy tissue cannot be excised with it, amputation is definitely indicated. In the past it has been our usage to recommend conservative treatment of small lesions, risking one recurrence and resorting to amputation if this recurrence appeared. In the light of the present findings, however, it would seem that this procedure is too hazardous and that extensive local removal or amputation should be resorted to at once.

Metastasis occurred in only one fifth of the cases. The lungs were the most frequently involved of the viscera. Metastasis of sarcoma to lymph nodes is not generally expected, yet it does occur. Willis<sup>7</sup> did not record any instances of metastasis of fibrosarcoma to lymph nodes. Stewart and Copeland<sup>3</sup> mentioned that it occurs but stated: "Dissemination to node areas is by way of venous emboli." Figure 8 shows metastasis to a lymph node. We have encountered other instances in cases not included in this study.

The location of the tumor may be of more importance than its histologic type. We have therefore presented our cases in relation to the point of origin, grouping those of tumor of the head, trunk, abdominal wall, breast, intra-abdominal region and extremities. This classification is particularly useful from the clinical standpoint.

When this division is made tumor of the head or face stands out as of particularly high malignancy, difficult to treat (table 7). There were twenty-four patients with such a growth, with an average age of 55.8 years; 58 per cent were males and 42 per cent females. The average duration of the disease was six and six-tenths years. The mortality was high in this group. Eight patients, or 33 per cent, are alive without recurrence, and only 21 per cent are living without disease after three years or more. Two additional patients are living with disease, one twenty-nine years after the onset, with eight recurrences through that period. One was a woman with a neurogenic fibrosarcoma

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7. Willis, R. A.: *The Spread of Tumors in the Human Body*, London, J. & A. Churchill, Ltd., 1934.

TABLE 7.—*Fibrosarcoma of the Head*

Case	Age, Yrs.	Sex	Duration to First Treatment, Mos.	Size	Location	Treatment	Number of Recurrences	Duration Since First Treatment, Years	Results			Pathologic Diagnosis
									Alive and Well, Years	Living With Disease	Died With- out Dis-	
1	53	♀	?	Large	Nasopharynx	Operation	8	29.0	...	+	..	Neurogenic fibrosarcoma
2	60	♂	6	Small	Under chin	Operation	0	15.0	15.0	..	..	Neurogenic fibrosarcoma
3	60	♂	?	Large	Nasopharynx	Operation	Several	1.1	...	..	..	Fibrosarcoma
4	61	♂	24	?	Parotid	Operation	0	12.5	14.5	..	..	Neurogenic fibrosarcoma
5	31	♂	3	Small	Tooth socket	None	0	9.5	12.5	..	..	Fibrosarcoma with tumor giant cells
6	58	♀	26	Large	Upper part of cheek	Operation	2	0.8	...	..	..	Neurogenic fibrosarcoma associated with the second division of the fifth nerve
7	60	♀	48	Large	Scalp	Radium; roentgen rays	0*	1.5	...	..	+	Fibrosarcoma
8	59	♀	?	Large	Nasopharynx	Operation	3	0.8	...	..	+	Fibrosarcoma with tumor giant cells
9	63	♂	60	Large	Upper lip	Roentgen rays; radium	6	6.0	11.0	..	..	Fibrosarcoma
10	72	♀	5	Small	Right brow	Operation	0	0.7	1.1	..	+	Fibrosarcoma with tumor giant cells
11	?	♂	24	Small	Lower middle gum	Operation	0	7.5	9.5	..	..	Fibrosarcoma
12	20	♂	2	Large	Gum	Radium	0*	0.3	0.4	..	..	Fibrosarcoma with tumor giant cells
13	49	♂	3	Large	Mouth	None	0	...	0.3	..	..	Fibrosarcoma
14	48	♂	102	Large	Nasopharynx	Operation	2	6.5	23.0	..	+	Fibrosarcoma, also epidermoid eardrum, grade I
15	72	♂	12	Small	Tongue	Operation	1	0.7	1.7	..	..	Neurogenic fibrosarcoma
16	33	♂	?	Large	Jaw	Operation	4	9.0	5.0	..	..	Fibrosarcoma
17	54	♂	?	Small	Right lid	Radium	5	8.5	...	..	..	Fibrosarcoma; this may be fibrosarcoma arising after irradiation; section from recurrent growth
18	43	♀	?	Small	Forehead	Operation	2	3.0	3.0	..	..	Fibrosarcoma with tumor giant cells
19	48	♀	1	Small	Mouth	Operation; roentgen rays	0	1.5	...	..	..	Fibrosarcoma with tumor giant cells
20	61	♀	1	Small	Upper jaw	Operation	3	0.8	0.9	..	..	Fibrosarcoma with tumor giant cells
21	64	♀	5	Small	Upper part of cheek	Operation	2	1.2	...	..	..	Neurogenic fibrosarcoma associated with the second division of the fifth nerve
22	78	♂	26	Small	Left lower lid	Operation	0	0	5.1	..	..	Myxofibrosarcoma
23	60	♂	36	Large	Upper part of cheek	Operation	2	5.5	3.0	..	..	Neurogenic fibrosarcoma
24	77	♀	8	Small	Face	Operation	0	0.8	0.8	..	..	Neurogenic fibrosarcoma with tumor giant cells

\* Persistence.

originating in the nasopharynx, who was 37 years of age when the disease first appeared. Half the tumors were noted as definitely small when first seen. The other half were fairly extensive. Four patients were treated primarily by irradiation, although operation was resorted

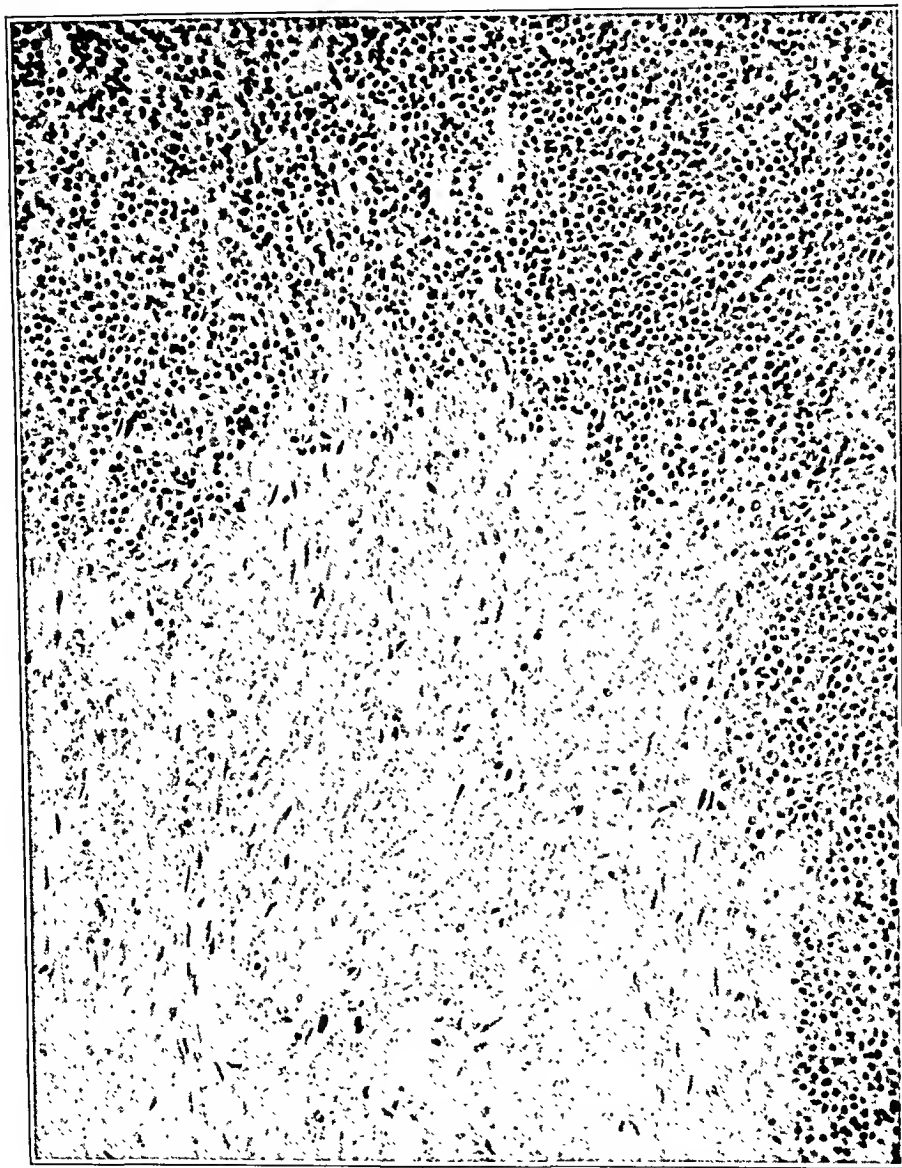


Fig. 8.—Section of fibrosarcoma metastatic to a lymph node. Hematoxylin-eosin stain;  $\times 120$ .

to for recurrence in two of these cases. All these patients who were treated by irradiation died with disease. In all but two of the cases in which recurrent tumors were treated roentgen therapy or radium was

utilized. One patient lived for eleven years and finally died with disease, having had two recurrences. One case is of particular interest in that there was a five year cure after four recurrences. Thirteen patients, or more than half, showed recurrence. In eight of these recurrence took place less than a year after the first treatment; in the case of four the time was unknown, and in one the recurrence was seven years after treatment of the primary tumor. As there was no biopsy of the initial tumor in the last-mentioned case, it is possible that it might be a fibrosarcoma that developed at the site of an irradiated cutaneous cancer of the face, although the assumption is that the earlier tumor was also a fibrosarcoma.

Only three patients showed metastasis, one to lymph nodes and one to the parotid gland and submaxillary nodes; the third showed generalized metastases. One instance of multiple tumor occurred in this group; in case 14 the neoplasm was an epidermoid carcinoma, of grade 1, of the oral mucosa, that developed adjacent to the fibrosarcoma of the nasopharynx. One probable myxosarcoma was found.

In eight of the cases the tumor was readily distinguished as a neurogenic fibrosarcoma on histologic examination. The average duration in these cases was nine and five-tenths years, or half again as long as that in the entire series of cases of fibrosarcoma of the head. In two cases the tumor was definitely associated with the second division of the fifth nerve, one growth ultimately extending along the course of the nerve to the gasserian ganglion.

The average duration in the cases of non-neurogenic tumor in this group was only four and two-tenths years. Here, then, is a distinct correlation between the length of life after the onset of disease and the histologic appearance of the tumor, the patients with well differentiated neurogenic fibrosarcoma showing an average duration twice as long as the group of those with fibrosarcoma and ten times as long as those with sarcoma with tumor giant cells. If one were to exclude from the instances of neurogenic tumor cases of fibrosarcoma showing tumor giant cells, the average duration would be even longer.

The malignancy in the cases of sarcoma with tumor giant cells is definitely much higher than that in the group as a whole, the seven patients with this type of tumor showing a total duration of the disease of only nine-tenths year after the onset.

Of the thirteen patients with fibrosarcoma of the head with recurrences, one patient had eight recurrences, one had six, one had five, one had four, two had three, five had two, one had "several" and one had one. Of the patients who had recurrences, three are living without disease, one five years and two less than a year after the onset. Two patients showed persistence of the tumor in spite of treatment.

Our largest group and perhaps the one of greatest practical importance to the surgeon is the cases of sarcoma of the extremities (table 8). There were sixty-two patients with an average age of 49.1 years; 52 per cent were males. The average duration of the disease was five and two-tenths years. The youngest patient, a male, showed a tumor of the right hand at birth. Excision was followed by twenty recurrences; the patient was treated by fourteen operations, considerable radium irradiation and finally amputation. He died with disease at the age of 16, of paralysis resulting from involvement of the spinal cord in the tumor. The next youngest patient, a girl of 7 months, is living and well thirteen years after operation. Fourteen patients, or 24 per cent, are living and well more than three years after the onset. None of these patients has had any recurrence. Thirty-two of the sixty-two patients, or over half, had recurrences, the number ranging from one to more than twenty.

Twenty-three patients in this group showed the presence of tumor giant cells on histologic examination. Of these, only five are living and well after three years, and for the eighteen who died the average total duration of the disease was only one and three-tenths years. This parallels the high malignancy of this form of tumor in other parts of the body.

In this group there were three instances of multiple tumor. One case, that of a 45 year old woman, is particularly interesting in that the metastases to the inguinal region were the first to attract attention, and only at the second operation was the primary tumor on the right small toe discovered and removed. The patient remained without evidence of the sarcoma for three and one-half years after operation but died of an extensive colloid carcinoma of the stomach after six operations for metastases.

The second case of multiple tumor occurred in a 29 year old woman with a neurogenic fibrosarcoma of the lower part of the leg and a carcinoma of the rectum, who died as a result of the carcinoma of the rectum three and five-tenths years after the operation for the neurogenic fibrosarcoma.

The third patient, an elderly woman, died with extensive fibrosarcoma of the left thigh and carcinoma simplex of the same location, presumably a metastatic lesion.

In an effort to determine what the influence of age might be, the patients over 65 years of age were selected. Of these, eight died with disease; three are living with disease, and only three are living and well after nine and eight-tenths years, one and seven-tenths years and seven-tenths years, respectively. Thus age is not a factor.



TABLE 8.—*Fibrosarcoma of the Extremities*

Case	Age, Yrs.	Sex	Duration to First Treatment, Mos.	Size	Location	Treatment	Number of Recurrences	Metastases	Duration Since First Treatment, Years	Results			Pathologic Diagnosis
										Alive and Well, Years	Living With Dis- ease, Yrs.	Died With Dis- ease, Yrs.	
1	41	♀	180	Small	Lower part of left leg	Operation	0	0	14.0	27.0	14.0	..	Fibrosarcoma
2	64	♀	?	Small	Upper part of arm	Amputation	0	0	10.8	10.8	..	10.8	Fibrosarcoma
3	?	♂	24	Small	Over tendon of quadriceps at left knee	Operation	0	0	13.0	15.0	..	..	Fibrosarcoma
4	0.7	♀	3	Small	Upper part of arm	Operation	0	0	12.7	13.0	12.7	..	Fibrosarcoma
5	59	♀	21	Small	Right deltoid region	Operation	0	0	12.0	14.0	12.0	..	Fibrosarcoma
6	13	♂	12	Small	Right forearm	Operation	0	0	10.7	11.7	10.7	..	Fibrosarcoma
7	30	♂	10	Large	Below elbow	Amputation	0	+	1.0	1.8	..	..	Fibrosarcoma
8	74	♂	36	Small	Right thigh	Operation	0	0	9.7	12.7	9.7	..	Fibrosarcoma
9	61	♀	30	Large*	Arm	Operation	1	+	1.0	3.5	..	..	Neurogenic fibrosarcoma with tumor giant cells
10	39	♂	3	Small	Left thigh	Operation†	8	0	3.0	3.2	..	..	Myxofibrosarcoma with tumor giant cells
11	36	♂	4	Small	Right groin	Operation†	0	0	0.2	0.5	..	..	Fibrosarcoma with tumor giant cells
12	0	♂	?	Small	Right hand	Operation	20	+	?	16.0	..	..	Fibrosarcoma
13	45	♂	20	Small	Right small toe	Operation	0	+	8.8	10.5	..	8.8	Myxofibrosarcoma
14	60	♀	12	Small	Right calf	Operation; recent. x-ray	0	0	9.7	10.7	9.7	..	Neurogenic fibrosarcoma
15	81	♀	10	Small	Left thigh	Operation	2	+	0.5	1.3	..	..	Giant cells
16	53	♂	4	Large	Lower part of right leg	Operation	4	0	0.7	1.0	..	..	Fibrosarcoma
17	45	♂	1	Small	Right forearm	Operation; recent. x-ray	0	0	8.5	8.6	8.5	..	Fibrosarcoma
18	37	♀	120	Small	Leg	Operation	0	0	8.2	18.2	8.2	..	Fibrosarcoma
19	45	♂	12	Small	Left thigh	Operation	4	0	8.0	9.0	0.1	..	Neurogenic fibrosarcoma with tumor giant cells
20	51	♂	7	Small	Right thigh	Operation	0	0	7.8	7.8	7.8	..	Neurogenic fibrosarcoma
21	70	♂	8	Small	Calf	Operation	1	0	0.2	0.9	..	..	Fibrosarcoma
22	55	♂	2	Small	Right thigh	Operation	6	0	7.7	7.9	0.1	..	Neurogenic fibrosarcoma
23	48	♂	18	Large	Right forearm	Amputation	0	+	1.0	2.5	..	..	Fibrosarcoma
24	29	♀	?	Small	Lower part of right leg	Operation	0	0	3.5	3.5	..	..	Fibrosarcoma
25	71	♂	2	Large	Right thigh	Operation	1	0	0.9	1.1	..	0.9	Neurogenic fibrosarcoma
26	67	♀	3	Large	Right thigh	Operation	1	0	0.7	0.9	..	..	Fibrosarcoma
27	76	♀	18	Large	Upper part of leg	Operation	2	+	1.5	2.9	..	..	Fibrosarcoma with tumor giant cells

TABLE 8.—*Fibrosarcoma of the Extremities—Continued*

28	49	♂	4	Large	Left forearm	Operation	1	+	0.5	0.8	...	...	+	Fibrosarcoma with tumor giant cells
29	?	?	24	Large	Left thigh	Operation	1	+	2.3	4.3	...	...	+	Fibrosarcoma with tumor giant cells
30	30	♂	141	Small	Over left deltoid	Operation	0	0	6.2	18.2	6.2	...	..	Neurogenic fibrosarcoma with tumor giant cells
31	55	♂	3	Small	Right thigh	Operation	1	0	5.3	5.5	5.0	...	..	Neurogenic fibrosarcoma with tumor giant cells
32	32	♂	4	Large	Right hand	Radium; operation	0†	+	1.4	1.7	...	...	+	Neurogenic fibrosarcoma with tumor giant cells
33	34	♂	?	Small	Foot	Operation	1	+	3.0	3.0	...	...	+	Neurogenic fibrosarcoma
34	66	♂	?	Small	Thigh	Operation	1	0	0.7	0.7	...	...	+	Neurogenic fibrosarcoma
35	22	♂	72	Small	Above left knee	Operation	2	0	8.0	14.0	1.7	...	..	Neurogenic fibrosarcoma
36	52	♀	?	Small	Right hand	Operation	1	0	5.2	5.2	5.0	...	..	Fibrosarcoma
37	?	?	12	Large	Left thigh	None	0	0	...	1.0	...	...	+	Fibrosarcoma with tumor giant cells
38	71	♂	12	Small	Right heel	Operation	1	+	1.1	2.1	...	...	+	Fibrosarcoma with tumor giant cells
39	29	♂	20	Small	Left groin	Operation	3	0	4.7	6.9	0.3	...	..	Neurogenic fibrosarcoma
40	46	♂	36	Large	Right knee	Operation	0	0	3.0	6.0	3.0	...	..	Fibrosarcoma with tumor giant cells
41	60	♂	3	Small	Right thigh	Operation	5	0	4.6	4.8	0.1	...	..	Neurogenic fibrosarcoma with tumor giant cells
42	58	♀	5	?	Right thigh	Operation	1	+	1.1	1.5	...	...	+	Neurogenic fibrosarcoma with tumor giant cells
43	?	?	3	Large	Right thigh	Operation	1	+	1.0	1.2	...	...	+	Fibrosarcoma with tumor giant cells
44	50	♀	4	Small	Upper part of left arm	Operation	0	0	1.8	2.1	1.5	...	..	Neurogenic fibrosarcoma
45	61	♂	18	Small	Groin	Operation; roentgen rays	0	0	0.7	2.2	0.7	...	..	Neurogenic fibrosarcoma
46	43	♂	5	Large	Left leg	Operation	1	+	1.9	1.3	...	...	+	Neurogenic fibrosarcoma with tumor giant cells
47	70	♂	4	Small	Lower part of right leg	Operation	1	+	0.5	0.8	...	...	+	Fibrosarcoma with tumor giant cells
48	11	♀	4	Small	Right knee	Operation	2	0	1.8	2.1	1.3	...	..	Neurogenic fibrosarcoma with tumor giant cells
49	21	♀	72	Small	Sole of foot	Operation	2	0	2.0	8.0	1.7	...	..	Neurogenic fibrosarcoma
50	50	♀	?	Small	Thigh	Operation	0	0	2.0	2.0	2.0	...	..	Neurogenic fibrosarcoma
51	70	♀	60	Small	Lower part of left leg	Operation	0	0	1.7	6.7	1.7	...	..	Neurogenic fibrosarcoma
52	47	♀	4	Large	Right thigh	Roentgen rays; operation	0†	+	1.5	1.8	...	...	+	Neurogenic fibrosarcoma; Recklinghausen's disease
53	76	♀	?	Large	Calf	Operation	1	+	1.3	1.3	...	+	..	Neurogenic fibrosarcoma
54	53	♀	3	Small	Over left deltoid region	Operation	0	0	2.7	2.9	2.7	...	..	Fibrosarcoma
55	29	♂	5	Large	Right thigh	Operation	1	+	1.2	1.6	...	...	+	Neurogenic fibrosarcoma with tumor giant cells
56	42	♀	7	Small	Upper part of left arm	Operation	2	0	1.8	2.4	0.7	...	..	Neurogenic fibrosarcoma
57	84	♀	0.5	Large	Leg	None	0†	0	...	0.1	...	...	+	Fibrosarcoma with tumor giant cells
58	38	♂	24	Large	Arm	Roentgen rays; amputation	0	0	0.7	2.7	0.7	...	..	Fibrosarcoma with tumor giant cells
59	67	♂	2	Small	Toe; sole	Operation	1	0	0.7	0.9	0.7	...	..	Neurogenic fibrosarcoma
60	75	♂	24	Small	Right knee	Operation	0	0	0.2	2.2	...	0.2	..	Neurogenic fibrosarcoma
61	65	♂	24	Small	Left thigh	Operation	4	0	1.4	3.4	0	...	..	Neurogenic fibrosarcoma with tumor giant cells; Recklinghausen's disease
62	23	♂	48	Small	Elbow	Operation	0	0	3.2	7.2	3.2	...	..	Neurogenic fibrosarcoma

\* Multiple tumors.

† Erysipelas and prodigious toxins.

‡ Persistence.

Thirty-one patients with neurogenic fibrosarcoma in this group showed no significant difference in total duration from the group as a whole, the figures for this group being four and seven-tenths years, as against four and nine-tenths years.

We encountered thirty-eight cases of sarcoma of the trunk exclusive of the tumor of the breast and of desmoid tumor of the abdominal wall (table 9). In approximately all the cases the tumor was of subcutaneous origin. The average age of the thirty-eight patients was 46.7 years; 63 per cent were males and 37 per cent females. The average duration of disease from the onset to death or the end of the follow up was four and eight-tenths years. Recurrence developed in fourteen cases, in eight in less than a year and in two additional cases in less than two years; in four cases the exact time of recurrence is unknown. Thus it will be seen that the time of recurrence corresponds closely with that in the cases of fibrosarcoma elsewhere and that a fair prognosis can be given for those patients who have lived one year without evidence of recurrent disease.

The danger of metastasis is apparently considerably over-rated here, as in the cases of fibrosarcoma of the extremities, as metastasis occurred in only six of the group, or 17 per cent. There is no significant difference between the behavior of the neurogenic sarcoma and the other types of fibrosarcoma so far as metastasis is concerned. One case (21), that of a 56 year old man in whom the tumor was primary in the anterior wall of the chest, is of particular interest in that the growth involved the axillary nodes. The extensive metastasis appeared only after a local recurrence. This patient is alive and well three and eight-tenths years after operative removal of the recurrent growth and the metastasis.

In nineteen cases the tumor could be recognized histologically as of neurogenic type, and the average total duration was of seven years. Fourteen patients are alive and well; seven, or 30 per cent, showed recurrence after more than three years; this is practically the same proportion as for the entire group, fourteen of thirty-seven. In some of the cases the tumor undoubtedly would not have recurred were it not for the inaccessibility of the lesion, which rendered complete operative removal extraordinarily difficult. Thus, in case 22, that of a man 37 years of age who had a small neurogenic fibrosarcoma of the upper part of the chest, apparently arising from an intercostal nerve, there were four recurrences over a period of five years, and the patient is living and well two months after the last operation, although it is probable that there may be another recurrence.

An illustration of the favorable outcome in a case of neurogenic fibrosarcoma, even when the tumor is extensive, is shown in case 36, that of a 26 year old man who had a neurogenic fibrosarcoma involving

the brachial plexus above and below the clavicle, which was very extensive when first seen, two years after symptoms were noted. Amputation of the shoulder girdle was done, and there has since been no recurrence or evidence of metastasis. The patient is living and well five and two-tenths years after the operation. Interestingly, this patient had coexistent active tuberculosis of the axillary nodes, and in the specimen removed at operation an intimate intermingling of the tuberculous process and the tumor was noted. Of the ten patients in this group who are living and well more than three years after the onset, four had recurrences (one patient had four, two had two, and one had one).

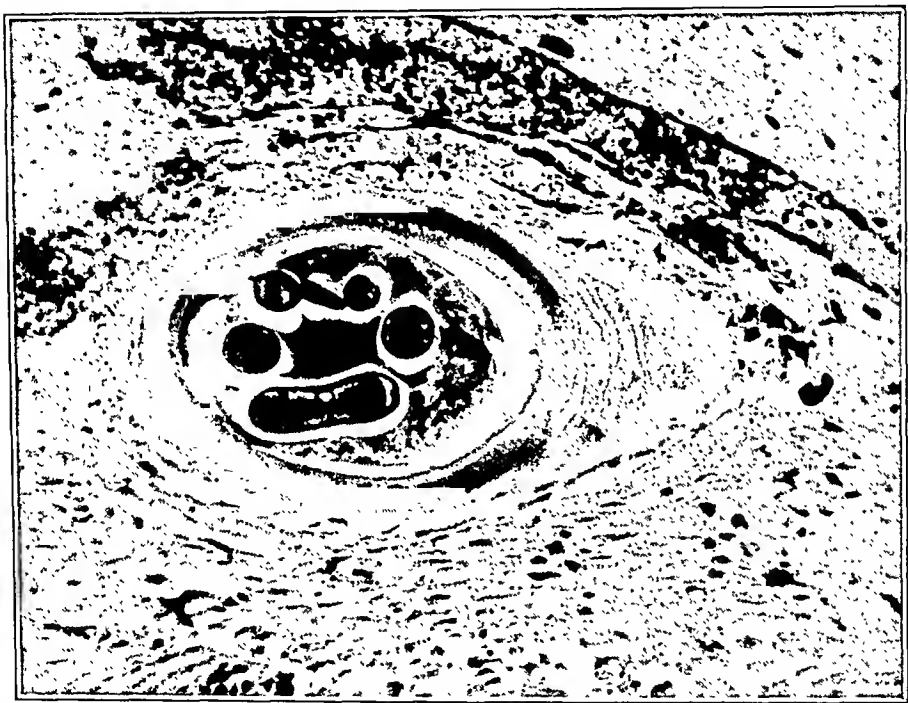


Fig. 9.—Section of fibrosarcoma of the shoulder, containing an encysted trichinella. Hematoxylin-eosin stain;  $\times 200$ .

All these were treated by operation, only one receiving roentgen treatment in addition to the operative procedure. The long duration in some of the cases is of striking interest; thus, in case 38, a man 42 years of age had a tumor of the right lower quadrant of the abdomen for fifteen years, which was treated by operation; four recurrent growths which were treated by both operation and the roentgen rays, and final metastasis to the lung after a total duration of twenty years.

The sarcoma with tumor giant cells maintained the same high level of malignancy as in other localities. There were eight cases of this type of growth, and only two patients are living and well, one after two and eight-tenths years, the other after six years. The average

TABLE 9.—*Fibrosarcoma of the Trunk*

Case	Age, Yrs.	Sex	Duration to First Treatment, Mos.	Size	Location	Treatment	Number of Recurrences	Metastases	Duration Since First Treatment, Years	Total Duration, Years	Alive Well, Years	Results	Pathologic Diagnosis
1	43	♀	1	Small	Left scapular region	Operation	1	+	0.4	0.5	....	.. .. +	Fibrosarcoma with tumor giant cells; also Trichinae in the tumor
2	37	♀	3	Large	Right gluteal region	Operation; incomplete	0	0	0.1	0.3	....	.. .. +	Fibrosarcoma with tumor giant cells; also adenocarcinoma of the uterus
3	13	♂	?	Small	Shoulder	Operation	0	0	12.7	12.7	12.7	.. ..	Neurogenic fibrosarcoma
4	42	♀	6	?	Right scapular region	Operation	0	0	2.0	2.5	....	.. .. 2.0	Neurogenic fibrosarcoma
5	63	♂	24	Small	Lumbar region	Operation; roent- gen rays	0	0	1.2	3.2	....	.. .. 1.2	Neurogenic fibrosarcoma
6	33	♀	?	?	Neck	Operation	4	0	31.0	31.0	9.0	.. ..	Neurogenic fibrosarcoma
7	49	♂	36	Small	Posterior part of axilla	Operation	0	0	10.0	13.0	10.0	.. ..	Neurogenic fibrosarcoma
8	55	♂	6	Small	Left lumbar region	Operation	0	0	2.5	3.0	....	.. .. +	Fibrosarcoma with tumor giant cells
9	50	♂	?	?	Right shoulder	Operation	1	0	8.2	8.2	8.2	.. ..	Neurogenic fibrosarcoma
10	48	♂	24	Small	Right scapular region	Operation; roent- gen rays	1	0	7.7	9.7	2.7	.. ..	Neurogenic fibrosarcoma
11	53	♂	2	Large	Anterior wall of chest	Operation; roent- gen rays	0	0	0.5	0.7	....	.. .. +	Fibrosarcoma
12	43	♀	12	Large	Shoulder	Operation; roent- gen rays; radium	2	0	1.2	2.2	....	.. .. +	Fibrosarcoma
13	37	♀	?	Large	Upper part of back	None	0	+	...	1.2 (?)	....	.. .. +	Neurogenic fibrosarcoma
14	60	♂	12	Large	Right buttock	Operation; roent- gen rays	0	0	6.0	7.0	6.0	.. ..	Fibrosarcoma with tumor giant cells
15	48	♂	60	?	Left shoulder	Operation	2	0	11.0	16.0	5.2	.. ..	Neurogenic fibrosarcoma
16	61	♀	12	Small	Neck	Operation	2	+	1.0	2.0	....	.. .. +	Fibrosarcoma with tumor giant cells
17	?	♂	?	Large	Back	Operation	0	0	5.3	5.3	5.3	.. ..	Neurogenic fibrosarcoma
18	55	♂	12	Small(?)	Side	Operation	0	0	1.5	2.5	....	.. .. 1.5	Neurogenic fibrosarcoma
19	?	♀	?	Small	Chest	Operation	1	0	5.5	5.5	....	.. .. +	Fibrosarcoma
20	26	♀	24	Small	Over sacrum	Operation	4	+	2.5	4.5	....	.. ..	Fibrosarcoma
21	56	♂	5	Small	Over left breast	Operation	2	+	4.0	4.4	3.8	.. ..	Fibrosarcoma with tumor giant cells
22	37	♂	2	Small	Upper part of right side of chest	Operation	4	0	4.8	5.0	0.2	.. ..	Neurogenic fibrosarcoma
23	70	♀	?	?	Above left clavicle	Operation	2	+	1.0	1.0	....	.. .. +	Neurogenic fibrosarcoma
24	27	♂	4	Small	Below left ear	Operation; radium	0	0	1.2	1.5	....	.. ..	Neurogenic fibrosarcoma
25	54	♂	?	Small	Right groin	Operation	5	0	3.2	3.2	0.2	.. ..	Neurogenic fibrosarcoma
26	55	♂	?	Small	Neck	Operation	0	0	1.8	1.8	1.8	.. ..	Fibrosarcoma
27	35	♂	12	Small	Over scapula	Operation	0	0	1.8	2.8	....	.. ..	Neurogenic fibrosarcoma
28	31	♂	1	Small	Over left breast	Operation	0	0	1.7	1.8	1.7	.. ..	Neurogenic fibrosarcoma
29	81	♂	24	Large	Right buttock	Operation	0	0	0.5	2.5	....	.. .. 0.5	Fibrosarcoma with tumor giant cells
30	30	♂	72	Large	Shoulder	Operation	0	0	0.3	3.3	0.3	.. ..	Neurogenic fibrosarcoma
31	37	♂	36	Small	Left buttock	Operation	0	0	0.5	6.5	....	.. ..	Fibrosarcoma with tumor giant cells
32	54	♀	?	Large	Pectoral fascia	Operation	0	0	0.3	3.3	0.3	.. ..	Fibrosarcoma
33	41	♀	?	Small	Labia	Operation	1	0	1.0	1.0	....	.. ..	Fibrosarcoma
34	50	♀	1	Small	Axilla	Operation	0	0	6.5	6.5	6.5	.. ..	Fibrosarcoma
35	?	♀	?	Small	Neck	Operation	0	0	0.5	1.5	0.5	.. ..	Fibrosarcoma
36	26	♀	24	Large	Brachial plexus	Operation; amputation of shoulder girdle	0	0	1.9	1.9	1.9	.. ..	Neurogenic fibrosarcoma; also tuberculous of lymph nodes
37	72	♂	?	?	Back	Operation; roent- gen rays	0	0	0.3	0.3	....	.. .. 0.3	Myxofibrosarcoma with tumor giant cells
38	12	♂	204	Small	Abdominal wall, right lower quadrant	Operation	4	+	3.7	20.0	....	.. .. +	Fibrosarcoma

: incomplete.

duration in the fatal cases was one and five-tenths years, as against four and three-tenths years for all tumors that were primary in the trunk.

A curious finding in one of the cases of fibrosarcoma with tumor giant cells, in which the growth developed in a 43 year old woman in the left scapular region, was extensive invasion of the fibrosarcoma with trichinas (fig. 9). Whether this was an actual invasion of the tumor by trichinas or whether it was caused by destruction of muscle in which the encysted organisms lay and subsequent inclusion in the growth of the tumor, it is impossible to say. We have observed trichinas in two other cases of malignant disease, one a case of osteogenic sarcoma of the humerus and the other a case of epidermoid carcinoma with extensive involvement of muscle.

One striking group is the cases of tumors within the abdomen and of the genitalia (table 10). The cases of undifferentiated retroperitoneal tumor are not included, only those in which the tumor grew definitely as fibrosarcoma being listed. There are twelve cases in the group, with an average age for the patients of 47.7 years and an average duration of the disease of two and seven-tenths years. One third of the patients were males. Two patients are living and well after three and eight-tenths years and six and six-tenths years, respectively; eight died with disease, and two are living with disease. The tumors in the latter cases are of interest, one because of extreme malignancy on histologic examination and rapid initial development, the other because of neural origin and very well differentiated structure, the growth being a fairly defined neurogenic fibrosarcoma. In one case (2) the first tumor developed in a 43 year old man and was primary in the prostate. Tumor giant cells, great mitotic activity and very poor differentiation pointed to a rapidly growing tumor. Recurrence took place within a month after the initial operation, but with the aid of repeated roentgen treatment the tumor has been held in check, and the patient has been living with disease, working most of the time, for seven and one-half years. When seen recently he had stopped work temporarily for a course of irradiation; a large pelvic mass was present. In contrast to this case is case 12, that of a 50 year old woman who had an extensive but well differentiated neurogenic fibrosarcoma involving the pelvic structures, who came for treatment three months after the development of symptoms; the tumor presented in the groin by extension through the obturator foramen. Incomplete operative removal aided by radium and the roentgen rays has held the tumor in check for a period of four and three-tenths years.

The desmoid tumor of the abdominal wall (table 11) constitutes a distinct type. In practically all cases such a growth arises from the region of the sheath of the rectus muscle. It occurs in relatively young

TABLE 10.—*Intra-Abdominal Fibrosarcoma*

Case	Age, Yrs.	Sex	Duration to First Treat- ment, Mos.	Size	Location	Treatment	Num- ber of Recur- rences	Durat- ion Since First Treat- ment, Years	Results				Pathologic Diagnosis	
									Total Dura- tion, Years	Alive and Well, Years	Living With Disease, out Years	Died With Dis- ease		
1	44	♀	9	Small	Abdomen	Operation	0*	0	0.9	....	7.5	..	+	Myxosarcoma with tumor giant cells
2	43	♂	1	Large	Prostate	Operation; gen rays	1	+	7.5	....	..	..	..	Fibrosarcoma with tumor giant cells
3	40	♂	?	Large	Mesentery	Operation; gen rays	1	0	1.2	....	..	..	+	Fibrosarcoma
4	49	♀	12	Large	Abdomen	Operation	1	+	1.8	....	..	..	+	Fibrosarcoma
5	54	♀	12	Large	Abdomen	Operation	0	+	1.0	....	..	..	+	Myxosarcoma
6	38	♀	6	Large	Mesentery	None	0	0	0.5	....	..	..	..	Neurogenic fibrosarcoma
7	42	♀	?	Large	Retroperto- neal region	Operation	0	0	3.3	3.3	..	..	..	Neurogenic fibrosarcoma
8	51	♀	4	Large	Retroperto- neal region	Operation	0	0	0.1	....	..	..	+	Neurogenic fibrosarcoma with tumor giant cells
9	56	♀	?	Small	Vagina	Palliative	0*	0	?	....	..	..	+	Fibrosarcoma; also epidermoid carci- noma, grade I, of the anus
10	64	♂	12	Large	Prostate	Operation; gen rays	0	0	0.8	....	..	..	+	Fibrosarcoma
11	41	♀	?	Large	Labium	Operation	0	?	6.5	6.5	..	..	..	Fibrosarcoma
12	50	♀	3	Large	Pelvis and groin	Operation; gen rays; radium	0*	0	4.3	....	4.3	..	..	Neurogenic fibrosarcoma

\* Persistence.

TABLE 11.—*Desmoid Tumors of the Abdominal Wall*

Case	Age, Yrs.	Sex	Dura- tion to First Treat- ment, Mos.	Size	Location	Treatment	Num- ber of Reur- rences	Durat- ion Since First Treat- ment, Years	Total Dura- tion, Years	Results			Pathologic Diagnosis		
										Alive and Well, Years	Living With Dis- ease Years	Died With- out Dis- ease			
1	31	♂	6	Small	.....	Operation; 8cn rays	0	0	2.1	2.6	2.2	..	..	..	Fibrosarcoma, desmoid type
2	25	♀	2.5	Small	.....	Operation	0	0	2.5	2.7	2.5	..	..	..	Fibrosarcoma, desmoid type; multi- ple growth; three malignant adenomas of the colon
3	53	♂	?	Small	.....	Operation	0	0	5.2	5.2	5.2	..	..	..	Fibrosarcoma, desmoid type
4	52	♂	?	Small	.....	Operation	0	0	4.5	4.5	4.5	..	..	..	Fibrosarcoma, desmoid type
5	29	♀	12	Large	.....	Operation	0	0	1.5	2.5	1.5	..	..	..	Fibrosarcoma, desmoid type

adults and responds uniformly well to treatment. While this type of tumor can be regarded as practically benign, since metastasis is virtually unknown and recurrence is rare, on histologic grounds it must be considered as a true sarcoma. We encountered only five cases of such tumor in our series; the average age of the patients was 38 years and the average duration of the tumor three and five-tenths years. One case was of special interest, as the tumor developed in the scar of a rectus incision. Resection of the entire large intestine had been carried out in a 22 year old woman for multiple polyposis with three distinct carcinomas of the large intestine. Three years after this series of operations the desmoid tumor developed in the scar.

A consideration of adenofibrosarcoma of the breast (table 12) perhaps does not belong in a discussion of fibrosarcoma in general; this tumor has been considered in a number of careful treatises. However, the seventeen cases encountered in this series are of sufficient interest to be placed on record in a rather cursory fashion. The average age of the patients was 54 years. All were females. Thirteen patients are living and well; one was lost for follow up; one died without disease after one and one-half years, and one died with disease seven months after the onset. The case of the patient who was lost for follow up is of great interest. An adenofibroma of each breast was removed by bilateral amputation five years before the development of the present tumor, which appeared in the scar. It is interesting to speculate whether this might have arisen from aberrant breast tissue or from a persistent remnant of one of the adenofibromas previously removed. The former possibility is strengthened by the location of the growth in the lateral portion of the scar. A point of practical importance is that of the eight patients on whom a radical amputation was done, including dissection of the axillary nodes, none showed any evidence of involvement of the lymph nodes.

Adenofibrosarcoma of the breast occurs at a considerably later age than does adenofibroma, and consequently the chief problem in differential diagnosis is to distinguish it from carcinoma. Because of its failure to metastasize to the axillary nodes this differentiation is of great practical importance. The gross appearance of such a tumor is helpful in differentiating it from carcinoma. It is usually large; it expands the surrounding tissue rather than shows the bands of stromal contraction characteristic of carcinoma; it is freely movable, even after it has reached a fair size, and on section it is soft and often succulent, sometimes with a translucent appearance and a somewhat botryoid tendency. From the extent of the tumors noted in our series we feel that the procedure of choice is simple amputation of the breast, with removal of the fascia overlying the pectoralis muscle. We have included one case in the group (17) that of a woman 67 years of age, whose tumor



TABLE 12.—*Adenofibrosarcoma of the Breast*

Case	Age, Yrs.	Sex	Duration to First Treatment, Mos.	Size	Location	Treatment	Num-ber of Recur-rences	Duration Since First Treatment, Years	Results				Pathologic Diagnosis
									Alive and Well, Years	Living With Dis-ease, Years	Died Without Dis-ease, Years	Died With Dis-ease, Years	
1	74	♀	1	?	Right breast	Excision	0	1.4	...	..	1.4	..	Fibrosarcoma with tumor giant cells
2	34	♀	6	Large	Left breast	Excision	0	...	...	..	..	..	Adenofibrosarcoma
3	49	♀	8	Large	Right breast	Excision	0	2.8	2.8	..	..	..	Adenofibrosarcoma
4	51	♀	36	Large	Left breast	Radical operation	0	3.8	6.8	..	..	..	Adenofibrosarcoma with tumor giant cells
5	50	♀	12	Large	Left breast	Radical operation	0	4.2	5.2	..	..	..	Adenofibrosarcoma
6	39	♀	?	Small	Right breast	Amputation; roentgen rays	0	4.0	4.0	..	..	..	Adenofibrosarcoma
7	48	♀	?	Large	?	Radical operation	0	3.3	3.3	..	..	..	Adenofibrosarcoma
8	66	♀	12	Large	Left breast	Amputation; roentgen rays	0	1.8	2.8	..	..	..	Adenofibrosarcoma
9	60	♀	1	Large	Right breast	Radical operation	0	2.2	2.3	..	..	..	Fibrosarcoma with tumor giant cells
10	42	♀	4	Large	?	Operation	0	0.3	0.6	..	..	..	Fibrosarcoma with tumor giant cells
11	59	♀	6	Small	Left breast	Radical operation	0	1.5	2.0	..	..	..	Adenofibrosarcoma
12	58	♀	0.5	Small	Right breast	Excision; roent-gen rays	0	1.0	1.0	..	..	..	Adenofibrosarcoma
13	47	♀	1	Large	Right breast	Excision	0	1.0	1.1	..	..	..	Adenofibrosarcoma
14	48	♀	1	Large	Left breast	Radical operation	0	1.0	1.1	..	..	..	Adenofibrosarcoma
15	60	♀	3	Small	Left breast	Radical operation	0	1.0	1.1	..	..	..	Adenofibrosarcoma
16	60	♀	3	Large	Left breast	Radical operation	0	3.4	3.6	..	..	..	Adenofibrosarcoma
17	07	♀	?	Small	?	Radical operation	0	7.0	7.2	..	..	..	Adenofibrosarcoma
						Radical operation	0	0.8	0.8	..	..	..	Neurogenic fibrosarcoma

TABLE 13.—*Cases of Fibrosarcoma of Special Interest*

Case	Age, Yrs.	Sex	Duration to First Treatment, Mos.	Size	Location	Treatment	Num-ber of Recur-rences	Duration Since First Treatment, Years	Results				Pathologic Diagnosis
									Alive and Well, Years	Living With Dis-ease, Years	Died Without Dis-ease, Years	Died With Dis-ease, Years	
1	25	♂	12	Large	Upper part of left thigh	Roentgen rays	0	6.5	7.5	..	..	..	Fibrosarcoma
2	64	♀	1 (?)	Large	Neck	Operation	2	...	...	..	..	..	Fibrosarcoma; also epidermoid carci-noma, grade I
3	18	♂	?	Small	Penis	Operation	0	0.6	0.6	..	..	..	Fibrosarcoma; also epidermoid carci-noma, grade I
4	62	♂	?	Small	Left side of nose	Operation	0	0.8	0.8	..	..	..	Fibrosarcoma; also basal cell carci-noma
5	74	♀	2 (?)	Small	Left side of chest	Operation	0	3.3	3.5	..	..	..	Fibrosarcoma; also epidermoid carci-noma, grade II

was somewhat suggestive of neurogenic fibrosarcoma rather than of adenofibrosarcoma. Certain tumors, purely fibroblastic, are undoubtedly growths in which the overgrowth of the connective tissue element has wiped out the glandular structure and has made them appear as fibrosarcomas. The gross characteristics and the clinical behavior of these tumors are in keeping with the adenofibrosarcoma rather than the fibrosarcoma of the trunk.

We have regarded five cases (table 13) as worthy of special attention and grouping, regardless of the location of the growth. The first (case 1) is that of a man, 25 years of age, in whom a benign giant cell tumor of the upper part of the left femur developed, with later involvement of the ilium. This tumor ultimately developed into a fibrosarcoma, and the patient died with disease seven and five-tenths years after the onset. This case has been reported in detail by Simmons.<sup>8</sup>

In another case (2) a fibrosarcoma developed in a woman 64 years of age in the scar left by lymphadenitis following measles that occurred in childhood. This scar had been extensively treated with tri-nitrophenol fifteen years before the development of the sarcoma, and it may perhaps be assumed that this stimulation, which had produced a severe burn, was the initiating factor in the development of the neoplasm.

In still another case the sarcoma arose in the stroma of an epidermoid carcinoma of the penis that had been treated unsatisfactorily in a piecemeal fashion over a period of five and one-half years. Ultimately fibrosarcoma of the stroma developed, being found by chance at amputation of the penis for the recurrent carcinoma. The sarcoma promptly recurred and metastasized widely, killing the patient with multiple metastases six-tenths year after its detection.

In the two remaining cases the tumor developed on the basis of roentgen and radium burns. The development of carcinoma from roentgen lesions is well recognized, while that of fibrosarcoma is less frequent and is ordinarily not given great weight in the differential diagnosis of postradiation cutaneous changes. In all these cases the tumor developed later after the initial irradiation, in one case occurring after fourteen years of roentgen and radium treatment of a basal cell cancer of the nose, and in another (case 5) occurring together with epidermoid carcinoma of the skin twenty-four years after roentgen treatment of a tumor of the breast. One other case, in which the tumor was at first diagnosed as fibrosarcoma and epidermoid carcinoma, was that of one of the pioneer roentgen workers, a man 52 years of age who had received roentgen burns twenty-three years before. He had had several fingers amputated. In this case there was involvement of both the epitrochlear and the axillary lymph nodes, there having been two operations for involvement

8. Simmons, C. C.: Surg., Gynec. & Obst. 53:469, 1931.

of the epitrochlear nodes and one for involvement of the axillary lymph nodes, followed by amputation of the shoulder joint. However, careful study has convinced us that this tumor is properly classified as one of the spindle cell carcinomas recently reported by Martin and Stewart.<sup>9</sup>

#### SUMMARY AND CONCLUSIONS

Data for one hundred and sixty-three cases of fibrosarcoma of the soft parts have been analyzed and presented.

Fibrosarcoma is not a disease of young persons, the mean age at onset in both sexes being about 50 years.

Trauma is not an etiologic factor in these cases.

Most patients have been treated by operation.

Radiation therapy has been disappointing.

The interval from the onset of symptoms to the beginning of treatment bears no definite relation to the outcome of the treatment.

The neurogenic fibrosarcoma may be recognized as a definite subtype.

The appearance of tumor giant cells indicates higher malignancy, as was evidenced by a higher mortality and a shorter duration of the disease in the cases studied.

Recurrence is frequent (sixty-four cases) and has grave prognostic significance. However, eight patients are alive and well three years after treatment of their last recurrence.

Recurrence usually is early and is rare after the first year.

Metastasis is infrequent (thirty-four cases) and usually occurs after local recurrence.

Metastasis is most frequent in the lungs and may involve regional lymph nodes.

Fibrosarcoma involving the head or neck is serious, only 21 per cent of our patients being alive and well three or more years after the onset.

Seventeen cases of adenofibrosarcoma of the breast are reported; all but one of the patients have recovered. Lymph nodes were not involved.

In two cases fibrosarcoma was apparently secondary to changes caused by irradiation.

Ten instances of multiple tumor were found—6 per cent of the total number.

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9. Martin, H. E., and Stewart, F. W.: *Am. J. Cancer* **24**:273, 1935.

# EFFECT OF FAT INTRODUCED INTO THE JEJUNUM BY FISTULA ON MOTILITY AND EMPTYING TIME OF THE STOMACH

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Although considerable experimental work has been done in the last decade on the question of inhibition of gastric motility by fat, with very suggestive results, little of this research has made use of the barium sulfate meal and fluoroscope. Because this method offers the best approach to normal conditions, with no disturbance of the nervous or muscular continuity of the stomach, it appears to be a logical means by which to observe this phenomenon of inhibition. Accordingly, making use of the barium sulfate meal and fluoroscope and with dogs as subjects, I undertook the study now reported. Since the upper portion of the small intestine is believed to be the site of formation of the inhibitory agent, I studied the effect produced on the emptying of a barium sulfate meal from the stomach by fat introduced into the jejunum by way of a fistula. The influence of various control substances in the jejunum was determined, and a comparison was made between the action of fat in the small intestine and that of fat in the stomach. The study was made under the direction of Dr. F. C. Mann and Dr. J. L. Collman.

The discovery that fats retard digestion can scarcely be said to be one of the contributions of modern medicine, since Aristotle<sup>1</sup> wrote of it; however, Ewald and Boas<sup>2</sup> (1885-1886) were apparently the first to enlighten the medical profession with accurate experimental data on this subject. They determined, by aspiration of the gastric contents at inhibited for two hours in the cul-de-sac when oil was placed in the greater various periods after a starch-paste test meal with and without oil had been given, that when the mixture contained oil digestion was delayed

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From the Division of Experimental Medicine, the Mayo Foundation.

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1. Aristotle, quoted by Cowie, D. M., and Munson, J. F.: An Experimental Study of the Action of Oil on Gastric Acidity and Motility, *Arch. Int. Med.* **1**:61-101 (Jan.) 1908.

2. Ewald, C. A., and Boas, J.: Beiträge zur Physiologie und Pathologie der Verdauung, *Virchows Arch. f. path. Anat.* **101**:325-375, 1885; Beiträge zur Physiologie und Pathologie der Verdauung: II., *ibid.* **104**:271-305, 1886.

and that free acid was rarely present within the first half hour after the meal was taken. They concluded that the oil was responsible for the deficiency in hydrochloric acid and that the strength of the hydrochloric acid bore a relation to the rapidity of emptying of the stomach.

Lobasov,<sup>3</sup> according to Pavlov,<sup>4</sup> experimenting in 1897 on dogs with esophageal and gastric fistulas and Pavlov pouches, showed that the nervous phase of gastric secretion in response to a sham meal was inhibited for two hours in the cul-de-sac when oil was placed in the greater stomach. Lintwarew<sup>5</sup> in 1903 found in dogs with duodenal and gastric fistulas that fat introduced either into the stomach or into the duodenum caused reflex closing of the pyloric sphincter for from 1 to 3 hours. He postulated that this effect of fat was chemical and not mechanical. Sokolov,<sup>6</sup> according to Babkin,<sup>7</sup> in 1906 prepared dogs by making both a gastric and a duodenal fistula and a Pavlov pouch in each and by excising the portion of stomach and duodenum between the two fistulas so that material in the stomach could not gain entrance to the duodenum. He found in these animals a marked variation in the effect of fat on gastric secretion produced in the Pavlov pouch by meat in the stomach depending on whether the fat was placed in the stomach or in the duodenum. There was no effect on secretion in the pouch when fat was placed in the stomach, but there was marked inhibition of secretion when fat was placed in the duodenum. Lönnqvist<sup>8</sup> corroborated this work shortly afterward and thus strengthened Sokolow's view that the inhibitory effect of fat arises in the duodenum and that not only the nervous phase of secretion but the gastric phase as well is inhibited by this agent. Pavlov, after correlating the work done in his laboratory by Lobasov, Lintwarew, Sokolow and Lönnqvist, explained this property of fat as "a reflex inhibition of the secretory process, the reflex not necessarily originating in the stomach." He doubted the mechanical explanation.

Cannon<sup>9</sup> in 1904, in his epochal experiments on digestion in cats, noted by means of the barium sulfate meal and fluoroscope that the average rate per minute of gastric peristalsis after a fat meal was

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3. Lobasov, I. O., quoted by Pavlov.<sup>4</sup>

4. Pavlov, I. P.: *The Work of the Digestive Glands*, ed. 2, London, Charles Griffin & Company, Ltd., 1910.

5. Lintwarew, S. J.: Ueber die Rolle der Fette beim Uebergang des Magen-inhalts in den Darm, *Biochem. Centralbl.* **1**:96-97 (Jan. 15) 1903.

6. Sokolow, quoted by Babkin.<sup>7</sup>

7. Babkin, P. B.: *Die äussere Sekretion der Verdauungsdrüsen*, Berlin, Julius Springer, 1914.

8. Lönnqvist, Bernt: Beitrag zur Kenntnis der Magensaftabsonderung, *Skandinav. Arch. f. Physiol.* **18**:194-262, 1906.

9. Cannon, W. B.: *The Passage of Different Food-Stuffs from the Stomach and Through the Small Intestine*, *Am. J. Physiol.* **12**:387-418 (Dec.) 1904. *The Mechanical Factors of Digestion*, New York, Longmans, Green & Co., 1911.

slightly less and the waves more shallow than when proteins or carbohydrates were ingested. In his classic work on hunger in 1916 Carlson<sup>10</sup> observed that oil as well as other substances introduced into the small intestine inhibited gastric hunger contractions and gastric tonus.

During the course of some experiments in 1925 on gastric secretion in dogs with the stomach and duodenum separated (Lönnqvist-Pavlov and Lönnqvist-Heidenhain pouches), Lim, Ivy and McCarthy<sup>11</sup> observed that the application of as much as 250 cc. of olive oil to the entire stomach did not affect the course of secretion. However, fat in the duodenum inhibited the secretion of the entire stomach pouch which was stimulated mechanically by distention with a balloon. Inhibition of motility in the autotransplanted pouches of dogs produced by placing fat in the main portion of the stomach led Farrell and Ivy<sup>12</sup> in 1926 to postulate with favorable experimental background that a humoral mechanism is responsible for such inhibition by fat. In a similar manner Feng, Hou and Lim<sup>13</sup> in 1929 demonstrated the inhibition of gastric secretion in autotransplanted pouches, and they came to the same conclusion as to the nature of the production of such inhibition.

That bile might be intimately concerned in the inhibition of gastric motility by fat was suggested when Still and Carlson<sup>14</sup> in 1929 produced immediate but temporary inhibition and great diminution of gastric secretory response to a test meal by intravenous injection of bile. However, Kosaka and Lim<sup>15</sup> in 1930 were unable to demonstrate such inhibition even with intravenous injection of toxic doses of bile.

Feng, Hou and Lim in 1929 injected into a vein of a dog with an autotransplanted stomach pouch lymph taken from the thoracic duct of another dog that had been fed a fat meal previously and observed no inhibition of gastric secretion in the pouch. Moreover, fat still inhibited the gastric motility of an animal with a fistula of the thoracic duct.

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10. Carlson, A. J.: *The Control of Hunger in Health and Disease*, Chicago, University of Chicago Press, 1916.

11. Lim, R. K. S.; Ivy, A. C., and McCarthy, J. E.: Contributions to the Physiology of Gastric Secretion: I. Gastric Secretion by Local (Mechanical and Chemical) Stimulation, *Quart. J. Exper. Physiol.* **15**:13-53, 1925.

12. Farrell, J. I., and Ivy, A. C.: Studies on the Motility of the Transplanted Gastric Pouch, *Am. J. Physiol.* **76**:227-228, 1926.

13. Feng, T. P.; Hou, H. C., and Lim, R. K. S.: Mechanism of Inhibition of Gastric Secretion by Fat, *Chinese J. Physiol.* **3**:371-380 (Oct.) 1929.

14. Still, Kathleen S., and Carlson, A. J.: The Motor and Secretory Activity of the Stomach During Acute and Chronic Obstructive Jaundice in Dogs, *Am. J. Physiol.* **89**:34-45 (June) 1929.

15. Kosaka, T., and Lim, R. K. S.: On Mechanism of Inhibition of Gastric Motility by Fat: Inhibitory Agent from Intestinal Mucosa, *Chinese J. Physiol.* **7**:5-11 (March 15) 1933.

These investigators concluded that the extrinsic nerves of the stomach were not essential in this inhibition by fat and suggested a humoral mechanism as the more logical explanation; also, that fat itself was not the inhibitory agent and that the agent was not transmitted through lymphatic channels.

Roberts<sup>16</sup> in 1931, working with normal subjects and with patients suffering from gastric disorder in various forms, confirmed the fact, by aspiration of a previously fed gruel meal, that oil inhibits gastric secretion and motility. He proved that the slow emptying was not secondary to the inhibition of secretion, and he believed that a colyone resulted from absorption of the oil in the duodenum which exerted a restraining influence on the gastric cells and motility.

Nothmann and Wendt<sup>17</sup> in 1932, using the barium sulfate meal and fluoroscope, with dogs as the subjects, found that olive oil delayed markedly the emptying time of the stomach. Ligation of the pancreatic ducts did not affect this normal reaction to fat. Following total pancreatectomy oil had no inhibitory action on the motility of the stomach, and it disappeared from the stomach in a shorter time than proteins, the disappearance of which was also slightly faster than normal. Insulin had no inhibitory effect on this rapid emptying of the stomach. A barium sulfate meal without fat left the stomach in the usual time after extirpation of the pancreas. Nothmann and Wendt concluded that inhibition by fat is regulated by the pancreas, and that it prevents overloading of the duodenum with fat. Since the nerves to the pancreas were necessarily disturbed by the operative procedure, the investigators could not determine whether this effect was of a hormonal or a nervous nature.

Kosaka and Lim<sup>18</sup> in 1930 prepared an olive oil extract of the upper part of the small intestine which on intravenous or subcutaneous injection inhibited gastric secretion following a test meal. Similar extracts made from the gastric mucous membrane were without effect. Continuing their experiments, Kosaka, Lim, Ling and Liu<sup>19</sup> in 1932 prepared a trinitrophenol concentrate of the aforementioned extract, which

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16. Roberts, W. M.: The Effect of Oils on Gastric Secretion and Motility, *Quart. J. Med.* **24**:133-152 (Jan.) 1931.

17. Nothmann, M., and Wendt, H.: Ueber eine regulatorische Funktion des Pankreas für die Magenentleerung nach Fettmahlzeit, *Arch. f. Exper. Path. u. Pharmacol.* **168**:49-56, 1932.

18. Kosaka, T., and Lim, R. K. S.: Demonstration of the Humoral Agent in Fat Inhibition of Gastric Secretion, *Proc. Soc. Exper. Biol. & Med.* **27**:890-891, (June) 1930.

19. Kosaka, T.; Lim, R. K. S.; Ling, S. M., and Liu, A. C.: On Mechanism of Inhibition of Gastric Secretion by Fat: Gastric-Inhibitory Agent Obtained from Intestinal Mucosa, *Chinese J. Physiol.* **6**:107-126 (Feb. 15) 1932.

they found to be most potent. They suggested that the inhibitory substance is for the most part present in normal intestinal mucosa in an inactive state and that after exposure to oil a certain proportion of the inactive substance is activated. They proposed that the substance be called "enterogastrone." In 1933 Kosaka and Lim,<sup>15</sup> using the trinitrophenol preparation from the upper part of the small intestine intravenously, found gastric motility inhibited in dogs with gastric fistulas studied by the balloon method. However, the action of the preparation did not even approximate the inhibition produced by oil given by mouth. They suggested that possibly the enteric reflexes entered into the inhibition as well as the chemical mechanism, so that the latter acting alone could not be expected to produce as marked a result as oil by mouth.

Quigley, Zettelman and Ivy<sup>20</sup> in 1934 determined by the balloon method that the intravenous introduction of fat, soap, glycerin and chyle from the thoracic duct, respectively, was without effect on the gastric motility of dogs. By giving five times the threshold doses of cholecystokinin and secretin, respectively, and observing the absence of alteration in gastric motility they demonstrated that these two substances are apparently not concerned in the mechanism of inhibition by fat. When the extrinsic nerves were removed as completely as possible from a dog's stomach the latent period in the response to fat was found to be slightly longer (4 minutes) than when the nerves were intact (1½ minutes). They also demonstrated by various operative procedures that the site of initiation is dependent on contact of the oil with the mucosa of the upper part of the small intestine. They concluded that inhibition of gastric motility by fat undoubtedly involves a humoral agent, probably a colyone, and that, although under normal circumstances both the nervous and humoral mechanisms are perhaps involved in the process, the latter can act in the absence of the former, a longer latent period being the only difference.

In 1933 Lim,<sup>21</sup> summarizing the results of research on the subject, concluded that fat inhibits gastric motility and both the nervous and chemical phases of gastric secretion. Neither a reflex adrenal secretion nor a nervous reflex is essential in the mechanism. He believed this to be a chemical process and that the agent would be found in the intestine. Lim postulated that one colyone is responsible for the inhibition of both gastric secretion and gastric motility by fat.

20. Quigley, J. P.; Zettelman, H. J., and Ivy, A. C.: Analysis of the Factors Involved in Gastric Motor Inhibition by Fats, *Am. J. Physiol.* **108**:643-651 (June) 1934.

21. Lim, R. K. S.: Observations on the Mechanism of the Inhibition of Gastric Function by Fat, *Quart. J. Exper. Physiol.* **23**:263-268, 1933.



## MATERIAL AND METHOD OF STUDY

Six normal, healthy adult dogs, three males and three females, ranging in weight from 7 to 22 Kg., were used in these experiments.

*Operation.*—The jejunum was transected 14 cm. distal to the ligament of Treitz. To produce a jejunal fistula the portion of intestine distal to the transection was brought to the skin in the superior part of the abdominal incision. After closing the proximal end of the transected jejunum, a side-to-side anastomosis was made between it and the other portion of jejunum about 25 cm. distal to the stoma of the fistula (fig. 1). The lumen of the anastomosis was about three times as large as the intestine at this point. All operations were performed under

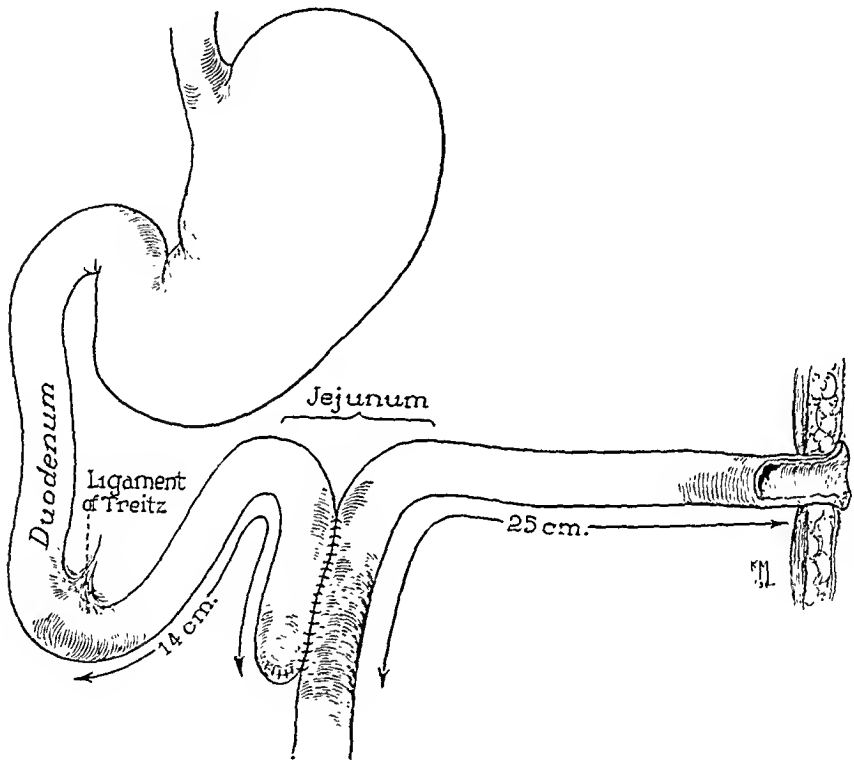


Fig. 1.—Method of making a jejunal fistula.

ether anesthesia, using surgical technic. All the dogs made an uneventful convalescence, and there was scarcely any leakage from the fistula; the dogs exhibited no signs or symptoms referable to the operative procedure and were apparently in normal health.

*Training.*—The dogs were made familiar with the observer, the passage of the stomach tube and the noises peculiar to the use of the fluoroscope. On no dog was an experiment begun until it was apparent that the animal was thoroughly familiar with the whole process; this required usually from 3 to 4 weeks of training. The dog was examined on the fluoroscopic table with loose restraining ropes on all four legs to hold it in position on its back. All the dogs remained quiet and composed during examination and made no effort to free themselves.

*Feeding and Care.*—The dogs were fed once daily by the observer a mixture of horse meat and cracker crumbs of twice the respective caloric requirement

for each dog at rest. They were taught to eat this meal immediately, and the food pan was shortly removed from the cage so that each animal was without food for 24 hours prior to the experiment. The dogs were fed at the same hour each day, except on those days on which observations were made, when they were fed at the completion of the experiment. No animal was put through the procedure oftener than every 48 hours. They were allowed water until 15 minutes prior to the introduction of the barium sulfate meal, but none after this time until emptying of the stomach was complete.

*Experimental Procedure.*—Each experiment was therefore started after the animals had been on a 24 hour fast. Thus the barium sulfate meal was given at the same time that the dog was usually fed. The opaque mixture was freshly made just prior to its introduction, and the amount was determined by the weight of the animal, 15 Gm. per kilogram of body weight being given. It was composed, by weight, of one-third barium sulfate, one-third acacia (10 per cent) and one-third skimmed milk (twenty-four hours old). These proportions of the ingredients produced a liquid mixture which readily ran down the lumen of a stomach tube of ordinary size. This mixture is referred to subsequently as the routine meal, and it was used in experimental series A, B, C, D and F. In series E the same amount of cream was incorporated with the barium sulfate meal as had been given by way of the fistula in series D; it was substituted for the skimmed milk in the mixture, so that the total volume was the same as that of the routine meal just described. However, the introduction of the cream into this mixture in series E produced such a thick gruel as to hinder the passage of the meal down the stomach tube. This necessitated reducing the barium sulfate portion by a third, which gave a meal of almost identical consistency with the routine meal.

All the animals were given the barium sulfate meal by tube. One dog would take the mixture voluntarily, thus affording an opportunity to compare the two methods of introduction as to any effect on the emptying of the stomach; no constant difference was noted. The amounts of the various substances placed in the jejunal fistula were determined also by the respective weights of the animals, approximately 5 Gm. per kilogram of body weight being used (100 Gm. for the two larger dogs, 50 Gm. for the two medium-sized dogs and 35 Gm. for the two smaller dogs). The material was always inserted into the fistula immediately prior to the barium sulfate meal in the stomach, never more than five minutes elapsing between the two maneuvers.

After the mixture had been placed in the stomach the animals were immediately examined fluoroscopically to determine the time of the first passage of material into the duodenum. If this did not occur within 10 minutes the dogs were returned to their cages and were examined at intervals of 15 minutes until the time of appearance of barium sulfate in the duodenum was determined. The dogs were then examined fluoroscopically every hour until the stomach was almost empty, after which they were examined at intervals of 30 minutes to determine as accurately as possible the gastric emptying time. Between observations the dogs were always placed in their cages in their usual surroundings.

## RESULTS

*Series A: Determination of the Normal Time of Appearance of the Routine Meal in the Duodenum and the Emptying Time of the Stomach.*

—After the postoperative convalescence and training period were com-

plete, the normal emptying time of the routine barium sulfate meal was determined for each of the six dogs by five satisfactory experiments. In series A nothing was inserted into the jejunal fistula.

The time of appearance of barium sulfate in the duodenum ranged from 4 to 33 minutes in the different animals, the average for each varying between 4.4 and 23.4 minutes. With the exception of one dog (M 195), the averages fell between 4.4 and 9.2 minutes, which is fairly uniform. The average emptying time with this mixture varied between 2 hours and 4.6 minutes and 3 hours and 31.6 minutes, the stomachs of the heavier dogs with the larger meals requiring longer to empty. Some of the animals were strikingly uniform in regard to the emptying

*A Comparison of the Average Time of Appearance of Barium Sulfate in the Duodenum and the Emptying Time of the Stomach (Series A, B, C, D and E)*

Dog	Weight, Kg.	Quantity in Fistula, Cc.		Series A		Series B		Series C		Series D		Series E	
				Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.
M 447	23	100	AP*	..	9.2	..	8.2	..	19.8	..	111.0	..	12.6
			ET†	3	31.6	4	36.8	4	18.8	8	12.0	7	36.6
M 690	18	100	AP*	..	8.0	..	9.4	..	18.2	..	98.0	..	14.0
			ET†	3	7.0	3	5.0	2	57.2	6	24.0	6	3.6
R 543	11	50	AP*	..	6.0	..	7.0	..	8.0	..	52.6	..	11.6
			ET†	2	36.0	3	5.0	2	51.8	5	45.6	5	7.2
R 377	10	50	AP*	..	6.6	..	6.4	..	17.8	..	58.0	..	14.4
			ET†	2	34.2	2	38.0	2	44.8	4	8.0	4	13.4
M 195	7	35	AP*	..	23.4	..	12.8	..	18.0	..	80.0	..	9.0
			ET†	2	48.4	2	38.8	2	58.0	5	9.0	4	54.0
R 540	7	35	AP*	..	4.4	..	7.6	..	10.6	..	44.6	..	8.2
			ET†	2	4.6	2	18.0	2	24.6	4	44.6	5	6.0

\* AP means appearance time; i. e., the time until barium sulfate was first seen passing down the duodenum.

† ET means emptying time; i. e., the time until the stomach was empty.

time of the stomach (R 540). One dog (M 690) varied as much as 1 hour from its average in one of the experiments (table and fig. 2).

Van Liere and Crisler<sup>22</sup> found the normal emptying time of the dog's stomach as observed by the fluoroscope to be remarkably uniform from day to day when all factors were kept constant. The extremes for a group of dogs varied from 5.42 to 8.07 hours, but these figures cannot be satisfactorily compared with mine since Van Liere and Crisler incorporated barium sulfate with a protein meal whereas the opaque mixture used in my experiments was comparatively inert. Ivy and Fauley,<sup>23</sup> using a different opaque mixture after a 24 hour fast, found the emptying of the dog's stomach as observed by the fluoroscope to vary from 4 hours and 10 minutes to 5 hours and 17 minutes.

22. Van Liere, E. J., and Crisler, G.: Normal Emptying Time of the Stomach of the Dog, *Proc. Soc. Exper. Biol. & Med.* **31**:85-87 (Oct.) 1933.

23. Ivy, A. C., and Fauley, G. B.: The Effect of Hunger on the Emptying Time of the Stomach, *Am. J. Physiol.* **91**:206-209 (Dec.) 1929.

*Series B: The Effect on the Time of Appearance of the Routine Meal in the Duodenum and the Emptying Time of the Stomach Produced by Placing Physiologic Solution of Sodium Chloride in the Jejunum.*—The procedure in this series of experiments differed from that in series A only in that varying amounts of physiologic solution of sodium chloride (35 to 100 cc., depending on the weight of the animal)



Fig. 2 (series A).—Emptying of the routine meal from the stomach. Nothing was introduced into the jejunal fistula. Upper left, 15 minutes; upper right, 1 hour and 20 minutes; lower left, 3 hours; lower right, 4 hours.

were placed in the jejunum by way of the fistula by slow injection through a soft rubber catheter. This immediately preceded the giving of the routine meal. Observations on the appearance time and emptying time were made exactly as in series A. The procedure was repeated for each animal until five satisfactory experiments were completed. The time of appearance of barium sulfate in the duodenum ranged from

5 to 21 minutes, the averages falling between 6.4 and 12.8 minutes. The average emptying time of the stomach varied between 2 hours and 18 minutes and 4 hours and 36.8 minutes for the different animals, which again demonstrated fair uniformity in the individual trials for each dog except for the experiments on the two larger animals, in which the emptying time varied 1 hour from the average (table).

In series B, in the majority of cases, there was a slight delay in the time of appearance of barium sulfate in the duodenum and a slight prolonging of the emptying time of the stomach as compared with the observations in series A. Since this delay was so insignificant and was not constant in all the dogs one must conclude that physiologic solution of sodium chloride in the jejunum as used in these experiments had little if any effect on gastric motility and emptying time.

*Series C: The Effect on the Time of Appearance of the Routine Meal in the Duodenum and the Emptying Time of the Stomach Produced by Placing Skimmed Milk in the Jejunum.*—Since the study of the inhibitory effect produced by fat in the jejunum was the primary object of these experiments, skimmed milk should be the ideal control to the cream used in the next series of experiments, D, as the only material difference between these two was in the higher fat content of the latter.

The procedure in this series of experiments differed from that in series B only in that skimmed milk was placed in the fistula instead of physiologic solution of sodium chloride. The appearance time varied from 5 to 32 minutes, the averages falling between 8 and 19.8 minutes. The emptying time averaged from 2 hours and 24.6 minutes to 4 hours and 18.8 minutes, likewise being fairly uniform from experiment to experiment in each case except in the largest animal, in which on one occasion the time varied by 80 minutes. There was a delay in the appearance time varying from 1 to 11.6 minutes in the different dogs, with an average delay of 6.8 minutes. In spite of this, there was no constant significant delay in emptying time when milk was used in place of physiologic solution of sodium chloride in the jejunal fistula (table and fig. 3).

In support of this delay in appearance of the barium sulfate, it is interesting that Carlson found that 10 cc. of milk (it was not stated whether it was whole or skimmed) in the duodenum inhibited hunger contractions in dogs for 30 minutes, which was longer than with any of the other substances tried. Thus it appears that skimmed milk introduced into the jejunal fistula definitely delays the first appearance of barium sulfate in the duodenum but has no appreciable constant effect on the time required for complete evacuation.

*Series D: The Effect on the Time of Appearance of the Routine Meal in the Duodenum and the Emptying Time of the Stomach Produced by Placing Cream (16 Per Cent Fat) in the Jejunum.*—The procedure in this series of experiments differed from that in series C only in the introduction of cream into the fistula just prior to the giving of the barium sulfate mixture by tube.

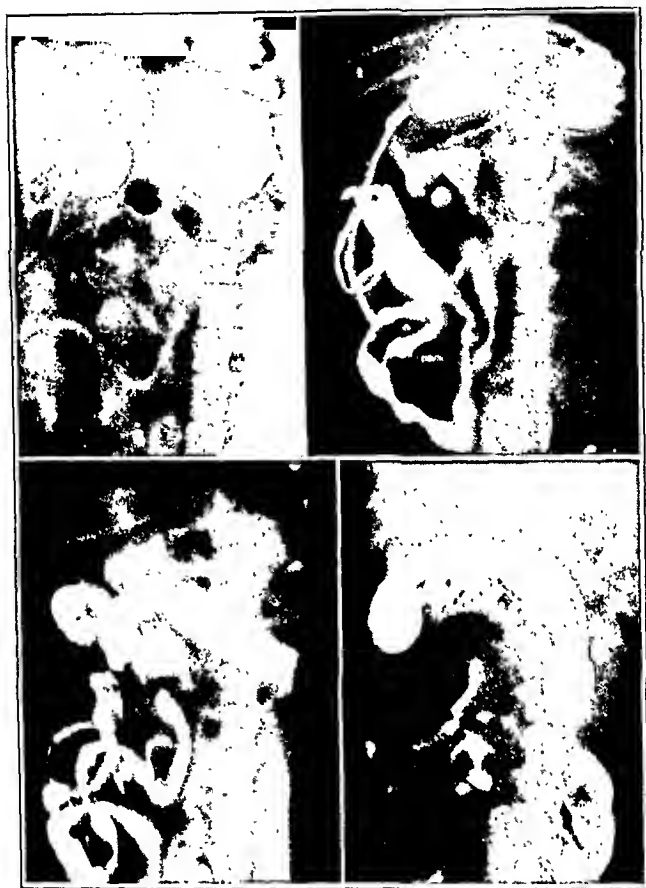


Fig. 3 (series C).—Emptying of the routine meal from the stomach after skimmed milk was placed in the jejunal fistula. Upper left, 15 minutes; upper right, 1 hour and 20 minutes; lower left, 3 hours; lower right, 4 hours.

At the first fluoroscopic examination, made within 5 minutes after the passage of the barium sulfate meal down the tube, there was marked atony of the whole stomach, and no peristaltic waves were discernible. This was in marked contrast to the usual findings with the preceding control meals (series A, B and C) in which active peristalsis, especially over the antral portion, was always present at this period and continued uninterrupted until emptying of the stomach was complete. With cream

in the jejunum, peristalsis did not appear until from 30 to 90 minutes (depending on the individual dog) after the entrance of the meal into the stomach. During the first few minutes the peristaltic waves were very shallow and never appeared throughout the delayed evacuation of the stomach to reach the depth they did in the first three series of controls.

The time of appearance of the barium sulfate in the duodenum was markedly delayed as compared with that in the control series A, B and C. The longest delay was 135 minutes; the shortest, 38 minutes. The average of the five experiments for each of the dogs ranged between 44.6 and 111 minutes. The total average delay in the appearance time for all the dogs caused apparently by fat in this series of experiments was 58.6+ minutes longer than that caused by the skimmed milk given in series C (table and fig. 4). The emptying time of the stomach was also markedly delayed by cream in the jejunum, being roughly almost 100 per cent longer than the time required in the control series (A, B and C). Compare figure 4 with 2 and 3. The emptying of the animals' stomachs was complete in from 3 hours and 50 minutes to 9 hours and 10 minutes. The averages for the respective dogs ranged between 4 hours and 8 minutes and 8 hours and 12 minutes.

It is quite important to note in series D that in spite of the handling on the fluoroscopic table and the frisking about of the dogs to and from their cages barium sulfate never was seen in the duodenum in less than 38 minutes. This seems to indicate that the inhibitory mechanism produced by fat owes part of its effect on the stomach to actual closure of the pyloric sphincter in addition to the atony and absence of peristalsis. If closure of the pylorus did not occur, some of the barium sulfate mixture would have been splashed or forced down the duodenum by gravity or by movements of the animal prior to this 38 minute period.

It is significant that Quigley, Zettelman and Ivy produced inhibition of hunger contractions in the dog for 40 minutes by placing cream in the jejunum. Thus it appears that fat in the jejunum causes marked delay in the initial appearance in the duodenum of material from the stomach as well as complete absence of peristalsis, giving way later to shallow waves that never reach the normal depth during evacuation. The emptying time is markedly delayed, and actual closure of the pylorus as part of the gastric inhibitory mechanism seems to be produced.

*Series E: The Effect on Gastric Motility and Emptying Time Produced by Incorporating Fat with the Barium Sulfate Mixture in the Stomach.*—The same amounts of cream were mixed with the barium sulfate meal as had been placed in the respective fistulas in series D. This cream was substituted for the skimmed milk used in the prepara-

tion of the routine meal, and the barium sulfate was cut down slightly until the volume and consistency of the meal were the same as those of the routine meal, and hence the meals could be compared. Nothing was introduced into the fistulas.

The first fluoroscopic examination after 5 minutes revealed active peristalsis of a good grade comparable to that in the control experiments. The time of appearance of barium sulfate in the duodenum varied in the different animals between 5 and 30 minutes, averages for the five experiments falling between 8.2 and 14.4 minutes. This finding was

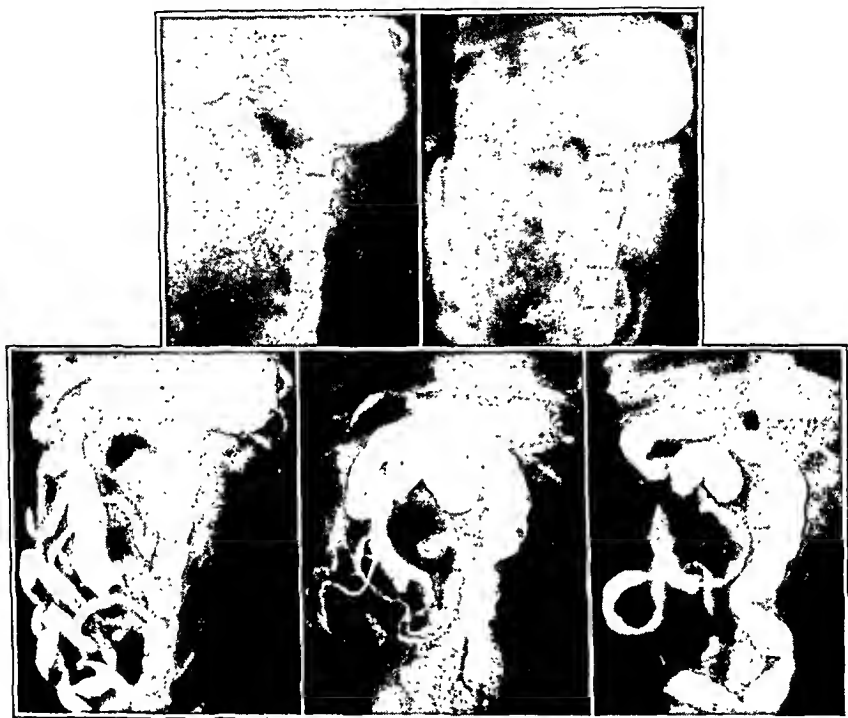


Fig. 4 (series D).—Emptying of the routine meal from the stomach after cream was placed in the jejunal fistula. Upper left, 15 minutes; upper right, 1 hour and 20 minutes; lower left, 3 hours; lower middle, 5 hours; lower right, 6 hours.

in marked contrast to the lack of peristalsis and the delayed appearance in series D, and it indicates that fat in the jejunum has a much quicker and more profound inhibitory effect than the same amount of fat in the stomach. It was only after a considerable amount of this barium sulfate mixture containing fat had passed into the upper part of the small intestine (in from 15 to 30 minutes) that inhibition of gastric peristalsis and of emptying became apparent, but it never equaled that produced by the same amount of fat in the jejunum. Peristalsis of a degree diminished from the normal continued until emptying was com-



plete. The emptying time varied between 8 hours and 15 minutes and 3 hours and 35 minutes; the averages were between 4 hours and 13.4 minutes and 7 hours and 36.6 minutes and thus were not materially different from those in series D (table and fig. 5).

Comparing the observations in series E with those in series D, it is apparent that there is, first, a profound and immediate effect of fat in the jejunum and, second, that there is a delayed effect of fat when it is in the stomach until a portion of it has reached well down into the



Fig. 5 (series E).—Emptying of a barium sulfate mixture of the same consistency and volume as the routine meal but in which was incorporated the same amount of cream as was used in series D. Upper left, 15 minutes; upper right, 1 hour and 20 minutes; lower left, 3 hours; lower middle, 5 hours; lower right, 6 hours.

upper part of the small intestine. This in addition to its weaker effect points to the site of formation of the inhibitory agent being in the upper part of the small intestine and not in the stomach. This conclusion was previously reached by Sokolow, Lönnqvist, Ivy and Lim after operative procedures on animals in which the nervous and muscular continuity had been disrupted. The experiments in the present study, however, demonstrate this seat of action of fat with the organs and

nerves undisturbed by any surgical procedures and by a method that at present produces as nearly normal physiologic conditions in the stomach as possible.

The question may well be raised whether or not the difference in concentration of the cream in the barium sulfate mixture when it was diluted one-third (series E) as compared with the undiluted cream in the fistula (series D) might not account for this difference in action of the fat at the two sites. To rule out this possible source of error, two additional control experiments, series F and series G, were undertaken.

*Series F: The Effect on the Time of Appearance of Barium Sulfate in the Duodenum and the Emptying Time of the Stomach Produced by Placing (1) Dilute Cream and (2) an Equivalent Quantity of Physiologic Solution of Sodium Chloride in the Jejunum.*—In each phase of this experiment five trials were run on one dog (M 195); the routine meal was placed in the stomach, and the usual observations were made. Cream of the same dilution that resulted after its incorporation with the barium sulfate mixture in series E (in this case 35 cc. of cream was diluted to 105 cc. by physiologic solution of sodium chloride) was placed in the fistula just prior to introducing the meal into the stomach. There was no material difference in the degree of inhibition produced by this dilution compared with the average figures when undiluted cream was used. Further, for purposes of control, 105 cc. of physiologic solution of sodium chloride was introduced into the fistula in place of the diluted cream, to show that it was not the quantity of solution introduced that produced the inhibition. This amount of physiologic solution of sodium chloride did not produce any more appreciable inhibition than the 35 cc. used in series B and nothing comparable to the inhibition produced by diluted cream. Diluted cream therefore appears just as efficacious in producing inhibition in the jejunum as the same amount of undiluted cream, both having an equivalent content of fat.

*Series G: The Effect on the Time of Appearance of Barium Sulfate in the Duodenum and the Emptying Time of the Stomach Produced by Placing Undiluted Cream in the Stomach.*—Three animals were used in this series, and five experiments were completed on each animal. The same amount of undiluted cream was placed in the stomach by way of a tube as had been placed in each of the respective fistulas of the animals in series D. One-third the usual amount of barium sulfate was incorporated with the cream, which made the mixture easily visible with the fluoroscope and of the same consistency as the routine meal.

The time of appearance of the meal containing undiluted cream in the duodenum did not vary appreciably from the averages when diluted cream was used.

Thus, since it is clear from the experiments in series F and G that the concentration or dilution of the same amount of fat does not alter its inhibitory power, it must be concluded from the observations in series D and E that the site of initiation for the gastric inhibitory mechanism is not in the stomach but in the upper part of the small intestine.

*Series H: The Effect on the Time of Appearance of Barium Sulfate in the Duodenum and the Emptying Time of the Stomach Produced by the Operative Procedure Used in Making the Jejunal Fistula.*—One animal (R 540) was used for these observations. After it had been trained, five satisfactory experiments with the routine meal were run before operation. After postoperative convalescence was complete a similar set of observations was made in which nothing was introduced into the fistula. There was no appreciable difference noted in the time of appearance of the barium sulfate in the duodenum or in the emptying time of the stomach after the establishment of the jejunal fistula as compared with the preoperative observations.

#### SUMMARY

With trained animals under controlled conditions the time of appearance of the routine barium sulfate meal in the duodenum and the emptying time of the stomach were fairly uniform. Physiologic solution of sodium chloride in the jejunum as used in these experiments had little if any effect on gastric motility and emptying. Skimmed milk in the jejunum caused an average delay of 6.8 minutes in the first appearance of material from the stomach in the duodenum. It did not appreciably lengthen the time required for complete emptying of the stomach. Cream (fat) in the jejunum immediately produced marked atony of the whole stomach with no peristalsis for from 30 to 90 minutes, depending on the quantity introduced and the size of the animal. The time of appearance of barium sulfate in the duodenum was markedly delayed by fat in the jejunum, averaging 58 minutes longer than with skimmed milk, and the emptying time of the stomach was prolonged. The gastric inhibitory effect of fat placed in the stomach was much less pronounced than that of a similar quantity of fat placed in the jejunum. The fat was apparently without effect until it had reached the upper part of the small intestine. It is suggested by the observations that there is actual closure of the pylorus and that this plays an important rôle in gastric inhibition produced by fat in addition to atony and absence of peristalsis. These experiments, employing a method that does not disturb normal physiologic conditions in the stomach, demonstrate that fat initiates its inhibitory action in the upper part of the small intestine and not in the stomach.

# SARCOMA OF THE STOMACH

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Frequently a pathologic condition considered rare in one generation and carefully studied and reported at that time appears to be more common in the following generation. The first case of sarcoma of the stomach was reported by Bruch<sup>1</sup> in 1847, and though subsequently many cases of this disease have been recorded in the literature, it is a relatively rare neoplasm which still eludes consideration from a diagnostic point of view, for in few of the reported cases was a diagnosis made before an operation or autopsy was performed. It is the object of this presentation to record a carefully studied case of sarcoma of the stomach in the hope that the correlation of the clinical data in this particular case with certain characteristic pathologic features of the disease may aid in its future clinical recognition.

The most comprehensive survey of the subject of sarcoma of the stomach which we have been able to find in the literature is that prepared by D'Aunoy and Zoeller,<sup>2</sup> who stated that 335 cases had been recorded up to and including the year 1929. They were able to review 135 case reports. Approximately 36 additional cases have been recorded since 1929, including 9 cases reported by Pack and McNeer<sup>3</sup> in May 1935. Balfour and McCann<sup>4</sup> presented the largest series from any one clinic, a group of 54 cases at the Mayo Clinic from January 1908 to July 1929. These 54 cases were extracted from a total of 4,159 cases of malignant lesion of the stomach, an incidence of 1 sarcoma to 111 carcinomas. More than half the cases reported by these authors were in men, whereas most other writers have found the incidence in men

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From the Department of Surgery, the New York Hospital and Cornell Medical College.

1. Bruch, Carl: *Die Diagnose der bösartigen Geschwülste*, Mainz, V. v. Zabern, 1847; quoted by Frazier, C. H.: *Sarcoma of the Stomach*, *Am. J. M. Sc.* **147**:781-788 (June) 1914.

2. D'Aunoy, R., and Zoeller, A.: *Sarcoma of the Stomach: Report of Four Cases and Review of the Literature*, *Am. J. Surg.* **9**:444-464 (Sept.) 1930.

3. Pack, G. T., and McNeer, G.: *Sarcoma of the Stomach: A Report of Nine Cases*, *Ann. Surg.* **101**:1206-1224 (May) 1935.

4. Balfour, D. C., and McCann, J. C.: *Sarcoma of the Stomach*, *Surg., Gynec. & Obst.* **50**:948-953 (June) 1930.

and that in women to be approximately equal. The average age was 43 years. In 1920 Douglas<sup>5</sup> reviewed 230 cases of sarcoma of the stomach in which the average age was 41.6 years, a figure considerably lower than that generally accepted for carcinoma.

Ewing<sup>6</sup> divided the sarcomas of the stomach into three distinct types: spindle cell myosarcoma, lymphosarcoma and miscellaneous round cell or alveolar sarcoma. He stated that the spindle cell myosarcoma forms "solid or cystic growths, single or multiple, which project from the wall of the stomach into the peritoneum, or remain interstitial or protrude into the cavity of the organ, where they suffer necrosis and ulceration." He pointed out that in the majority of cases the tumor arises from a curvature rather than from the pylorus. In describing the manner of growth he added that a large sarcoma is often cystic and tends to form bulky metastases in the liver, which likewise frequently become cystic and may even transform the organ into a series of large cystic tumors. He emphasized the fact that the differential diagnosis of spindle cell sarcoma and myosarcoma is frequently difficult and tends to vary with different observers.

Kaufmann,<sup>7</sup> in discussing the site of origin of the lesion in the wall of the stomach, stated that in the great majority of cases the tumor arises in the submucosa or muscularis, a tumor arising from the subserosa or mucosa being rare. He pointed out that a sarcoma which occupies chiefly the inner layers and is of the round cell type may be difficult to differentiate from a round cell carcinoma. However, as an aid to differential diagnosis, he emphasized the fact that these sarcomas "do not select the pylorus so frequently; they are oftener a clinically demonstrable tumor, show less tendency to ulcerate, are less malignant and usually of longer course; sometimes they reach the size of a man's head and a weight up to 12 pounds, which never happens with carcinomas." Kaufmann observed a myosarcoma of the stomach as large as a child's head, with enormous metastatic lesions in the liver. He pointed out that metastases appear in approximately one third of the cases of sarcoma of the stomach, most frequently in the regional lymph nodes and the liver but occasionally in other organs. A histologic classification was given in 100 of the tumors in the 135 cases reviewed by D'Aunoy and Zoeller, as follows: 63 per cent, lymphosarcoma and round cell sarcoma; 14 per cent, fibrosarcoma and spindle cell sarcoma, and 9 per cent, myosarcoma. In Balfour and McCann's group of 54 cases

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5. Douglas, J.: *Sarcoma of the Stomach*, *Ann. Surg.* **71**:628-638, 1920.

6. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 277.

7. Kaufmann, E.: *Pathology*, translated by S. P. Reimann, ed. 8, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 1, p. 690.

there were 45 in which operation was performed and microscopic examinations were reported. The diagnoses in these cases were as follows: lymphosarcoma, 71.3 per cent; fibrosarcoma and spindle cell sarcoma, 13.3 per cent, and myosarcoma, 6.7 per cent. It appears from these observations that the myosarcomas constitute a relatively small group.

Most observers have agreed that sarcoma of the stomach in general is more readily removed at operation and metastasizes later than carcinoma, thus offering a better operative prognosis. Surgical intervention appears to be more remedial for myosarcoma and fibrosarcoma than for lymphosarcoma and small round cell sarcoma.

The detailed report of the case presented is as follows:

#### REPORT OF A CASE

The patient was a 48 year old American-born housewife. She came to the medical outpatient department of the New York Hospital for the first time on Jan. 22, 1934, complaining of abdominal distention, epigastric distress, belching and abdominal cramps of one and one-half years' duration.

*Family History.*—The patient's mother died at the age of 49, having had inflammatory rheumatism. She was said to have had psychopathic tendencies for many years. The patient's father died of abscess of the lung at the age of 64. There were no brothers or sisters. The patient's paternal aunt died of tuberculosis, and the patient was exposed to this disease only when on occasional visits. Her maternal uncle was said to have had heart disease. The husband had always been well. The patient had one child, who died of quinsy when 2 months old. There were no other pregnancies. There was no family history of diabetes, cancer, gout or renal disease.

*History.*—The patient was born in New York and had always lived in the vicinity. She had been married for twenty-one years. The only illnesses which she was able to recall were whooping cough, measles, scarlatina and influenza. Apart from the fact that she worried a great deal about her mother's condition and about financial matters, her general health had been good until the onset of the present illness.

There were no symptoms referable to the head and neck except rather frequent headaches in the supra-orbital region, which started six months before her admission to the clinic. She had not complained of pain in the chest, and only on rare occasions did she have a cold accompanied with a mild cough. No sputum, hemoptysis, asthma or hay fever had been noted. Night sweats were associated only with the present illness, as were precordial pain, heart burn, dyspnea and palpitation. There was never any cyanosis or edema of the ankles. Beginning two years before the patient's admission to the clinic her husband noticed that her face was puffy and swollen on occasions, the condition being most noticeable when she arose in the morning and disappearing during the course of the day. This symptom, however, gradually disappeared. The menstrual cycle commenced when she was 12 or 13 and occurred every twenty-one days, each period lasting for two or three days. The flow was scanty. The last menstrual period was in January 1933. There was never any marked leukorrhea. There were no symptoms referable to the neuromuscular system. She abstained from the use of alcohol,

tobacco, tea and coffee. Her best weight was 145 pounds (66 Kg.) many years before her admission to the clinic. She gradually lost weight over a period of years and attributed this largely to worry. Her average weight in recent years had been 118 pounds (53.5 Kg.). At the time this record was made it was 120 pounds (54.5 Kg.).

*Present Illness.*—In 1929 the patient began having periodic attacks of moderately severe generalized abdominal pain which became localized in the left upper quadrant of the abdomen and persisted for two or three days. There were no associated symptoms until two years before her admission to the clinic, when she had an attack of diarrhea lasting for ten days. There was no evidence of blood in the stools at this time. About September 1932 she noticed while bathing an unusual fullness in the epigastrium. She was advised by her physician to have roentgenograms made. This was done by a chiropractor, and the films were read by her physician, who reported that no abnormality was revealed. After this she had several chiropractic treatments. After each of three of these manipulations the patient fainted. However, she thought that the lump had disappeared. One month later she was again aware of the mass and also of a dull, continuous pain in the left upper quadrant of the abdomen. At first the pain seemed to be relieved somewhat by the ingestion of food. At this time she began having severe abdominal cramps, but her physician is said to have reported that physical examination revealed no abnormality. Shortly after she commenced having abdominal cramps, she began to be troubled a great deal with gas on the stomach, the discomfort being relieved by belching. Meanwhile, the tumor progressively increased in size. A few months before her visit to the hospital she began eliminating various articles from her diet in an attempt to relieve the epigastric distress. As far as she could remember she had vomited only two or three times in her life, and on these occasions there was no evidence of blood in the vomitus. She had always been constipated but had never noticed any tarry, bloody or clay-colored stools. She could not recall that the skin ever had a yellowish tint. Her symptoms became steadily worse after the onset of the present illness. As the tumor became larger she was aware of increasing dyspnea and palpitation on slight exertion, and she complained of heart burn and precordial pain after the ingestion of food. For two or three months before her admission to the clinic she had been having occasional night sweats and had noticed that she was not as strong as she had been formerly.

*Physical Examination.*—The patient was a thin but fairly well developed white woman, lying comfortably in bed. The skin was clear, and the mucous membranes had a good color. The skull, scalp and hair were normal, and there was no tenderness over the sinuses. The auricular canals and drums were not unusual, and hearing was not impaired. The pupils were equal, and they reacted to light and in accommodation. The external ocular movements were normal. The arteries of the fundus showed slightly increased light reflexes. Examination of the nose revealed no obstruction, discharge or defect of the nasal septum. The teeth and gums were in good condition. The tongue was slightly coated, and the tonsils were small and buried. The pharynx was not injected. There was no stiffness or rigidity of the neck, and no general glandular enlargement was noted. The thyroid gland was not enlarged. The chest was narrow and thin walled. The lungs expanded equally, and the breath sounds were clear throughout. The cardiac apical impulse was weak and diffuse. There were no thrills, and the heart was not enlarged to percussion, the left border being 9 cm. from the midline. The sounds were of good quality, and there were no cardiac murmurs. The radial

arteries were somewhat thickened. The veins in the neck were moderately distended. The blood pressure was 118 systolic and 70 diastolic. The breasts were small and atrophic. No nodules could be palpated.

The abdomen was greatly enlarged and protuberant, and the veins in its upper portion were prominent. There was a large mass filling most of the abdomen in a symmetrical fashion. In some areas this mass felt solid, but in others it felt distinctly cystic. It was not tender. The upper border was continuous with the costal margin across the entire abdomen. The lower border was sharply defined and irregular in contour. It extended across the entire lower portion of the abdomen, well below the level of the umbilicus. The greatest diameter of the tumor was from the xiphoid process to the border of the tumor, a distance of 22 cm. The greatest circumference of the abdomen was 76 cm. The whole mass descended with inspiration. The liver and spleen could not be identified. Below the border of the tumor there was evidence of only a small amount of free fluid within the abdominal cavity. The kidneys were not palpable. On pelvic examination the uterus was of normal size, mobile, retroverted and retroflexed. The adnexa were not felt. There were no palpable masses within the rectum. The reflexes were normal. The extremities were not unusual. There was no edema.

*Course.*—The patient was advised to enter the hospital for treatment but at this time refused to do so. Between the date of her first visit to the clinic and her admission to the hospital, more than two months later, investigation was continued at the clinic. On Jan. 23, 1934, the blood count showed: erythrocytes, 3,860,000; white blood cells, 9,200, and hemoglobin, 77 per cent. The differential smear showed: adult polymorphonuclears, 49 per cent; immature polymorphonuclears, 8 per cent; monocytes, 5 per cent; lymphocytes, 30 per cent; eosinophils, 5 per cent, and basophils, 3 per cent. On repetition the results were approximately the same. The Kline and Wassermann tests of the blood were negative.

On January 22 a proctoscope was passed for a distance of 25 cm. and revealed no abnormality. This was repeated with the same result on the following day.

On February 16 stool culture for *Endamoeba histolytica* gave negative results. On February 17 gastric analysis showed 30 degrees free acid and 45 degrees total acid. Roentgen examinations during this period gave the following results: On January 24 a barium sulfate enema showed that the colon was normal. On February 15 the stomach and duodenum were observed to be distorted by extrinsic pressure. The cardiac end of the stomach was compressed by a mass which was thought to be an enlarged spleen. The lower end of the stomach was depressed by a mass which was thought to be the liver. There were no intrinsic filling defects. The six hour examination revealed a small amount of barium retained in the stomach, the head of the barium meal being in the splenic flexure; the twenty-four hour examination showed that the colon was normal. On March 10 a similar examination revealed the same picture. A flat plate of the chest showed that the diaphragm was high, but it was otherwise normal. The hepatic shadow showed no areas of increased or decreased density, and the liver appeared to be diffusely enlarged. On February 7 a cholecystogram failed to show a definite shadow of the gallbladder. The test was repeated on February 25, with a doubled oral dose of the dye, and the result was the same.

On March 27 the patient prevailed on to enter the medical ward for observation. Since her first visit to the clinic the symptoms had progressed, but she was still able to be up and about. She commenced having mild chills and slight fever on occasions. She was able to take only a small amount of food at a time because of the epigastric distress and fulness which eating produced. The



mass was increasing in size. A film of the chest at this time showed no evidence of a primary growth or metastases. A flat plate of the abdomen revealed a mass occupying most of the upper three fourths of the abdomen and pressing down on the transverse colon. In the lateral view the mass was seen to occupy the anterior position. Films of the lumbar region of the spine and sacrum showed no metastatic lesions. Examination of the urine on one occasion revealed slight albuminuria, with occasional red and white blood cells and no bile. On a second occasion the urine was normal. The red blood cell count varied between 3,200,000 and 4,200,000. There were 10,500 leukocytes, and the hemoglobin value was 63 per cent. The differential smear was normal. The Kline test was repeated and again showed a negative result. The urea nitrogen content of the blood was 10 mg. per hundred cubic centimeters, and the sugar content 87 mg. The icteric index was 15 and 7.5. The van den Bergh test showed negative results. Gastric analysis showed no free hydrochloric acid in the fasting specimen and a maximum of 10 one hour after the ingestion of 30 cc. of 7 per cent alcoholic solution. There was no blood in the specimen. The patient remained in the hospital for a period of ten days, and during this period there was a slight daily elevation of the temperature. The skin showed a questionable subicteroid tint. The patient's condition was variously diagnosed as primary carcinoma of the liver, Banti's disease, cystic kidney and pancreatic tumor. The surgeon, called in consultation, favored the diagnosis of pancreatic cysts and advised laparotomy. However, the patient refused any kind of operation. She was discharged on April 6 and was instructed to return to the clinic in three weeks.

The patient did not report to the clinic, and we were unable to follow the course until she was brought to the accident room on August 18, when she was seen to be in a grave condition. She was immediately admitted to the surgical service. In the interval of four and one-half months the abdominal mass had progressively increased in size and had gradually become painful, especially during the two weeks preceding the patient's admission to the hospital. Her appetite had slowly failed, and she was unable to take more than a small quantity of food at a time. Constipation persisted. There were no tarry, clay-colored or bloody stools or vomiting. The patient had not noted any jaundice. Dyspnea and palpitations became extreme on slight exertion. Weakness was progressive, but she weighed 3 pounds (1.3 Kg.) more than on her first visit to the clinic. Although she was weak, she was able to be up and about most of the time until two weeks before admission to the hospital, when she caught cold and was forced to stay in bed until she was brought into the hospital. During these two weeks there was a persistent elevation of temperature. The physical examination gave the same results as the previous one except for these facts: The general appearance was obviously that of a gravely ill woman. Slight exertion was difficult for her. The abdominal mass had greatly increased in size. The lower border was still clearly defined and irregular in contour. It extended to about 6 cm. above the pubis. Palpation again revealed solid and cystic areas. The mass was not tender. It descended with inspiration. The veins in the upper part of the abdomen were more distended than they had been at the time of the first examination. The skin and scleras showed no icteroid tint.

Examination revealed that the urine was normal. The red blood cell count varied between 3,500,000 and 2,500,000, and the leukocyte count, between 33,500 and 41,500. The differential smear showed that most of the polymorphonuclear leukocytes were of the immature type. Chemical analysis of the blood showed: urea nitrogen, 12 mg. per hundred cubic centimeters; sugar, 60 mg.; calcium, 9

mg., and phosphorus, 3.8 mg. The icteric index was 6. A flat plate of the abdomen revealed the same picture as on the previous occasion, except that the mass had increased in size. A film of the chest showed that the diaphragm on the right side was high. The costophrenic angles on both sides were obscured, but the fields of the lungs were not otherwise unusual. A barium enema corroborated the results of the previous examinations, which showed that the colon was normal. Unfortunately, the patient was too ill for a repetition of the entire gastro-intestinal examination. After admission to the ward the patient failed rapidly. The temperature rose gradually in steplike formation. The second day after her admission to the hospital she was unable to take anything by mouth, and on the fifth day a definite yellowish tint was observed in the skin.



Fig. 1.—Photograph of the gross specimen of leiomyosarcoma of the stomach with massive metastases to the liver.

This steadily deepened. Fluids were administered by infusions and clyses. Weakness became extreme, and on August 26 the temperature rose to 42.5 C. (108.5 F.), and the patient died.

*Postmortem Examination.*<sup>8</sup>—The body was that of a white woman of the intermediate anatomic type, considerably undernourished. The weight was 116 pounds (52.5 Kg.). The skin and scleras were slightly icteric. There was moderate edema of both lower extremities. Thrombosed external hemorrhoids were present. The peritoneal, pleural and pericardial cavities contained 150, 100 and 75 cc., respectively, of clear, watery yellow liquid. General routine examination revealed no other unusual features.

8. The autopsy was performed by Dr. H. S. Dunning, of the department of general pathology.

Stomach and Liver (see the drawing of the gross specimen, fig. 1): The upper portion of the abdominal cavity was occupied by a huge, roughly oval tumor, measuring 30 cm. in the longitudinal axis of the body, 17 cm. in the transverse axis and 10 cm. in the anteroposterior axis. It lay between the two layers of the lesser omentum between the stomach and the liver. These peritoneal membranes were tightly stretched over its *anterior and posterior surfaces*. The mass occupied a position over the anterior aspect of the stomach, duodenum and pancreas, which were flattened. It had compressed the left, the caudate and the quadrate lobe of the liver, pushing them forward and upward, thus elevating the diaphragm. The



Fig. 2.—Drawing of the gross specimen of leiomyosarcoma of the stomach with massive metastases to the liver

mass was attached to the liver by delicate fibrous adhesions. It had pressed the spleen into the extreme upper left portion of the abdominal cavity and had displaced the transverse colon and the greater omentum downward into the lower portion of the abdomen. The tumor was directly continuous with the wall of the stomach, which it replaced in a round area, 5 cm. in diameter, in the anterior portion of the cardia just below the esophagus. Here the tumor projected slightly into the gastric cavity and was covered only with thin, transparent mucosa, except where the tumor tissue formed the walls of two round ulcers, 1.6 and 0.5 cm. in

their respective diameters. Squeezing the tumor caused the exudation of gray, putrid-smelling, thick liquid, containing shreds of dead tissue, from the inside of the mass through these holes into the gastric cavity. Sectioning showed that the whole center of the tumor was necrotic, thus producing a cystic structure the wall of which was composed of ivory-colored, homogeneous, firm tissue containing numerous hemorrhages. This wall was in some places only 2 cm. in diameter. Numerous round circumscribed masses of the same tissue were embedded in the liver. They varied in diameter from 5 mm. to 12 cm. The largest mass

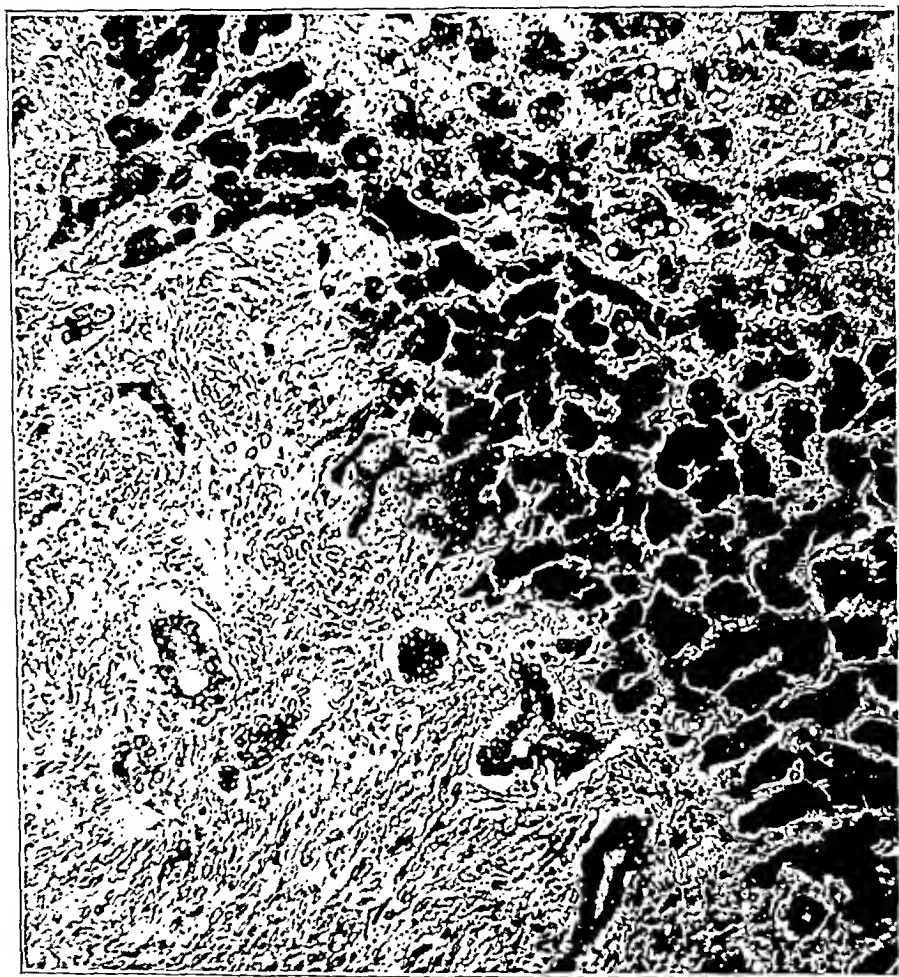


Fig. 3.—Metastasis to the liver. The tumor lies in Glisson's capsule, where it is not encapsulated but fades off into the surrounding parenchyma. Throughout the masses of tumor cells are proliferating bile ducts similar to those seen in cirrhotic processes.

occupied the midportion of the right lobe of the liver and consisted of a shell of tumor substance filled with watery blood and necrotic tissue. The parenchyma of the liver between the tumor nodules was congested. The gallbladder and the cystic, hepatic and common bile ducts, portal vein and hepatic artery were normal. The hepatic, splenic and celiac lymph nodes were normal.

Microscopic examination showed that the primary tumor in the stomach occupied the musculature of the organ, lying in the muscle coats and pushing out the muscularis mucosae and the mucosa before it. The mucosa was necrotic and formed the bed of an ulcer which extended down into the tumor. Large spheroidal masses of tumor cells lay between the ulcer and the serosa and spread out on either side. They were surrounded by thin capsules which seemed to be composed of muscle strands rather than of connective tissue.

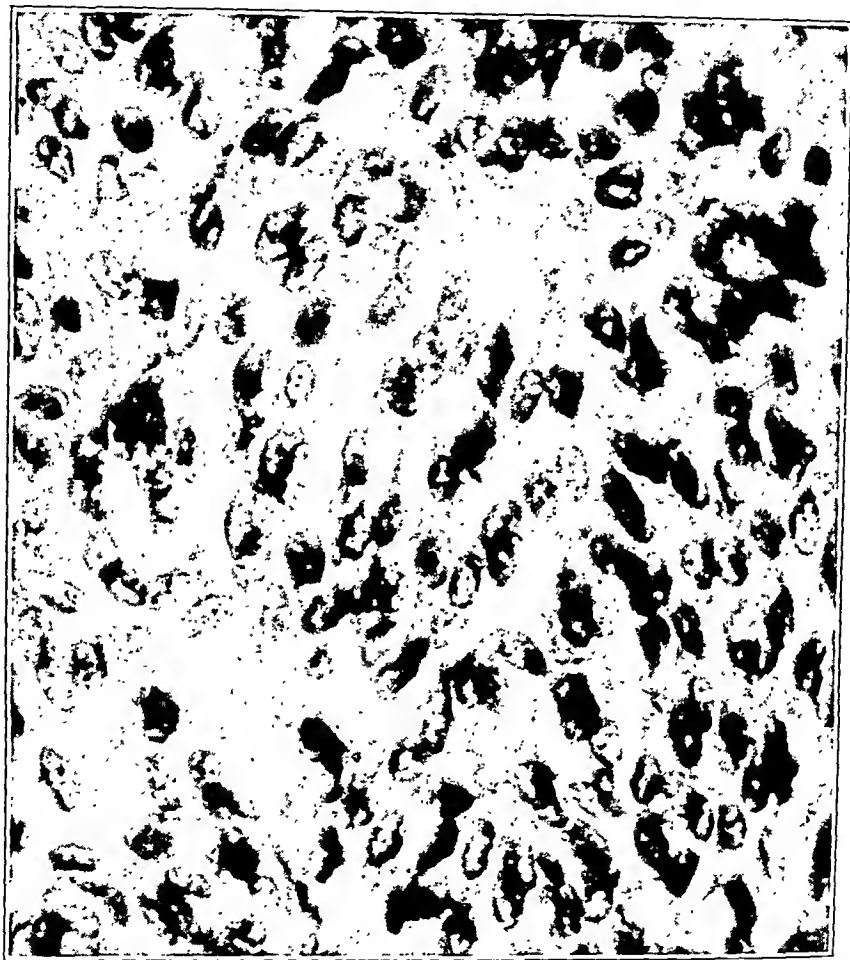


Fig. 4.—Photomicrograph of the primary tumor in the stomach.

The metastasis in the liver (fig. 3) lay in Glisson's capsule, where it was not encapsulated but faded off into the surrounding parenchyma. Throughout the masses of tumor cells were proliferating bile ducts similar to those seen in cirrhotic processes.

Microscopic examination<sup>9</sup> of the leiomyosarcoma of the stomach (fig. 4) showed that it was composed of more or less spheroid masses of cells that lay in bundles or leashes. With the hematoxylin and eosin stain the cells showed a rather stout body with processes that extended outward and anastomosed with similar processes

9. Dr. Nathan Chandler Foot made the microscopic study of the tumor.

from neighboring cells, the cytoplasmic material forming a vacuolated network of intercellular bridges. This was reminiscent of the appearance of embryonal smooth muscle. The cytoplasm was acidophilic, pink with eosin, red with Mallory's connective tissue stain and with Masson's trichrome process and reddish yellow in phosphotungstic acid and hematoxylin preparations. The nuclei were hyperchromatic and elliptic, with gently rounded poles like those of smooth muscle cells, not tapering and pointed like those of fibroblasts. Mitotic figures were not seen, in spite of prolonged searching. Tumor giant cells that exactly resembled the type cell but were about twice its size were occasionally present. The stroma was composed of collagenous tissue and was not copious. Instead of running around and between the cells, as it would in the case of the matrix of a fibrosarcoma, it tended to outline the cell bundles like a sheath. This was only occasionally well developed, and there were areas where the connective tissue had become massed into scarlike septums and partitions in the tumor. This was particularly true of the unit masses already described, and these were surrounded with connective tissue sheaths or capsules that were thin and often broken through.

*Diagnosis.*—From the arrangement of the cells, the location of the tumor in the musculature of the stomach, the presence of gently rounded elliptic nuclei and the tendency of the cells to anastomose and form a cytoplasmic reticular syncytium, one may deduce that this was a leiomyosarcoma rather than a fibrosarcoma. This assumption is further strengthened by the great scarcity of mitotic figures, which is a rather commonly encountered phenomenon in a leiomyosarcoma and unusual in a rapidly growing fibrosarcoma.

#### COMMENT

The outstanding clinical features of this case are as follows: (1) the absence of vomiting, (2) the lack of evidence of bleeding into the gastrointestinal tract, (3) the failure to demonstrate by roentgen examination a filling defect in the stomach, (4) the absence of appreciable jaundice until two days before death and (5) the fact that the patient gained 3 pounds (1.3 Kg.) in weight during the terminal seven months of the illness.

These circumstances, which must be considered unusual in connection with a gastric lesion, may be explained in the following manner: 1. The tumor involved only a small area of the gastric wall and projected mainly outside the stomach; therefore there were no symptoms of obstruction. 2. The mucosa of the stomach was little involved; therefore, there was no demonstrable bleeding into the gastro-intestinal tract. 3. Not only was the mucosa little involved, but the cavity of the stomach was not deformed by a mass, so that no actual filling defect was shown roentgenographically. 4. In spite of the extensive replacement of hepatic tissue by tumor, there remained, it must be assumed, sufficient hepatic substance to prevent the development of jaundice until the absorption of necrotic, infected primary and metastatic growth caused symptoms of toxemia. 5. The gain in weight in a patient who was

apparently moribund was explained at autopsy by the presence of a large amount of fluid in the peritoneal cavity and by the weight of the primary and secondary tumors.

#### CONCLUSION

A case of leiomyosarcoma of the stomach in an advanced stage is described, with full clinical and autopsy reports. When one is confronted with an epigastric tumor, even in the absence of obstruction, without demonstrable filling defects on roentgen examination and without bleeding into the gastro-intestinal tract, it is important to bear in mind the possibility of sarcoma of the stomach, particularly if the patient is in the fourth or fifth decade of life.

# A NEW TEST FOR EVALUATING CIRCULATION IN THE VENOUS SYSTEM OF THE LOWER EXTREMITY AFFECTED BY VARICOSITIES

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AND

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NEW ORLEANS

It has been forty-five years since Trendelenburg<sup>1</sup> (1891) reemphasized the most important factor concerned in the disturbance in function of varicose veins of the lower extremity. In this paper he demonstrated incompetence of the valves of the internal saphenous vein and the reversal of circulation that results, i. e., the peripheral flow of blood in the superficial venous system. Moreover, he popularized an operation<sup>2</sup> which is the most direct attack on the physiopathologic factor, namely, ligation and section of the long saphenous vein to prevent the blood from spilling from above through the saphenous vein into the varicosities. The good results he obtained with this operation in a large series of cases were later reported by Perthes.<sup>3</sup> Since that time much has been added to the knowledge of individual methods and combinations of methods for the treatment of varicose veins, and the problem has been shown to be not so simple or easy of solution as perhaps appeared to Trendelenburg and Perthes. The trends and changes in the methods of managing varicose veins have been numerous, and today the question as to the best method is by no means settled; the last chapter has not been written. Sometimes fatalities, but usually recurrences—disappointments that followed in the wake of each enthusiastically received new method of management—resulted in further search for a safe, simple way of permanently curing varicose veins. So far none has proved to be satisfactory, though undoubtedly today the surgeons most skilful in the knowledge and technic of the best procedure indi-

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1. Trendelenburg, F.: Ueber die Unterbindung der Vena saphena magna bei Unterschenkelvaricen, Beitr. z. klin. Chir. **7**:195, 1891.

2. According to Trendelenburg, others, including Ambroïse Paré, had ligated the internal saphenous vein for relief from varicosities.

3. Perthes, Georg: Ueber die Operation der Unterschenkelvaricen nach Trendelenburg, Deutsche med. Wchnschr. **1**:253, 1895.



cated in the individual case secure better and more lasting results than have most workers in the past. Only to the inexperienced will this particular phase of the practice of the art of healing seem simple and easy and without the amenities of study-stimulating complexity and its at least intellectual recompense.

So many variable factors are active in the production of varicose veins that a number of different types or patterns require individual methods of management. In order to treat intelligently a patient with varicosities of the lower extremity a survey by certain tests is necessary to evaluate the condition of the circulation in the superficial and deep veins and in the communicating veins. In the surgical clinic of the Tulane University School of Medicine we employ as a routine the tests to be described, and sometimes others less helpful, in every case of varicose veins of the lower extremity before outlining the plan of treatment. One of these methods (described last) is a test which we developed and the information it furnishes is important in planning the proper management of the particular condition and in predicting the dangers of recurrence.

#### TESTS FOR EVALUATION OF CIRCULATION IN VARICOSE VEINS

1. *Trendelenburg Test*.—This test was adequately described<sup>4</sup> forty-five years before the appearance of the paper by Trendelenburg. It is applied thus: The patient reclines on a table. One leg is elevated to the vertical position and is supported in this position for a few minutes in order to empty the superficial veins. The leg is lowered to the dependent position, and the patient rises to the sitting and then to the standing position. The varicosities distend quickly if the valves of the internal saphenous vein are incompetent, owing to the unresisted rush of blood from the femoral vein through the saphenous veins. The patient again assumes the reclining position, and the leg is elevated. The fingers of the observer are placed over the upper end of the vena saphena magna, and firm pressure is applied. The leg is lowered to the horizontal position, and the patient swings around and stands on the floor while the fingers are still so firmly applied that they prevent movement of

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4. The method was described by Sir Benjamin Brodie (Lectures Illustrative of Various Subjects in Pathology and Surgery, London, Longmans, 1846, vol. 7) as follows: "If I put on a bandage and squeezed the blood out of the veins below and then put my thumb on the vena saphena above so as to stop the circulation through it, I found on taking off the bandage, the patient being in the erect posture, that the cluster of veins below filled very slowly and only from the capillary vessels; but if the patient be in the erect position, I removed the pressure from the veins, the valves being of no use the blood rushed downward by its own weight contrary to the course of the circulation and filled the varicose cluster below almost instantly."

the blood through that segment of the vein. As soon as the patient is in the erect position the observer fixes his attention on the degree of prominence shown by the veins of the calf and lower part of the thigh. If the pressure is maintained, the varicose veins fill slowly from below. When the pressure on the saphenous veins is suddenly released the rapidity with which the varicosities fill is noticed. If the veins suddenly fill and bulge as though the blood has been dumped into them, it indicates incompetency of the valves of the long saphenous vein. Later, a further evolution of this test came to be known, the source of which is obscure. If the pressure on the saphenous vein is maintained and the varicosities fill rapidly—more rapidly than might be expected to occur through the capillaries alone (which takes about thirty-five seconds)—the interpretation is made that the varicose veins fill from incompetent collaterals below the point of pressure (fig. 1). Thus, when the Trendelenburg test shows incompetence of the saphenous valves and the secondary test more rapid filling than usual, indicating incompetence of the valves of the communicating veins, the reaction to the Trendelenburg test is said to be doubly positive.

A doubly positive Trendelenburg reaction is of significance. It indicates retrograde flow from the deep to the superficial system, not only through the main entrance of the long saphenous vein into the femoral vein but through the communicating channels below between the deep and the superficial system. Prior to development of the test to be described later there was no accurate way of determining whether the communicating veins with incompetent valves were in the thigh or calf or both. In an excellent paper published in 1910 Moro<sup>5</sup> stated that incompetency of the valves of the communicating veins is not always diagnosed clinically. He found that the Trendelenburg operation failed to effect cure in 55 per cent of the cases in his series and expressed the belief that the failure was due to incompetency of the valves of the communicating veins, which he attempted to remedy by further surgical procedure. His criterion for incompetency of the valves of the communicating veins was only a postoperative observation, viz., that ligation of the internal saphenous vein did not cure the condition in certain of his cases (55 per cent), resulting in little if any improvement in the condition in these instances. Homans<sup>6</sup> in 1916 expressed greater appreciation of the method for preoperative diagnosis of incompetence of the valves of the communicating veins on the basis of the doubly positive reaction to the Trendelenburg test. Since that time authors

5. Moro, G.: Ueber die Pathogenese und die zweckmässigste Behandlung der Krampfaden der unteren Extremitäten. Beitr. z. klin. Chir. **71**:420, 1910.

6. Homans, J.: The Operative Treatment of Varicose Veins and Ulcers Based on a Classification of These Lesions, Surg., Gynec. & Obst. **22**:143, 1916.

have been aware of this way of determining incompetence of communicating veins below the opening of the saphenous vein.

2. *Perthes' Test*.—Perthes called attention to the fact that benefit is to be derived from ligation and section of the long saphenous vein in the cases in which diminution in the size of the varicose veins is shown when the patient walks with a tourniquet around the thigh or with pressure applied by the patient's fingers over the long saphenous vein sufficient to compress it. The test is applied thus: With the patient standing, a rubber tourniquet is tied securely around the thigh sufficiently tight to obstruct the flow of blood in the superficial venous sys-

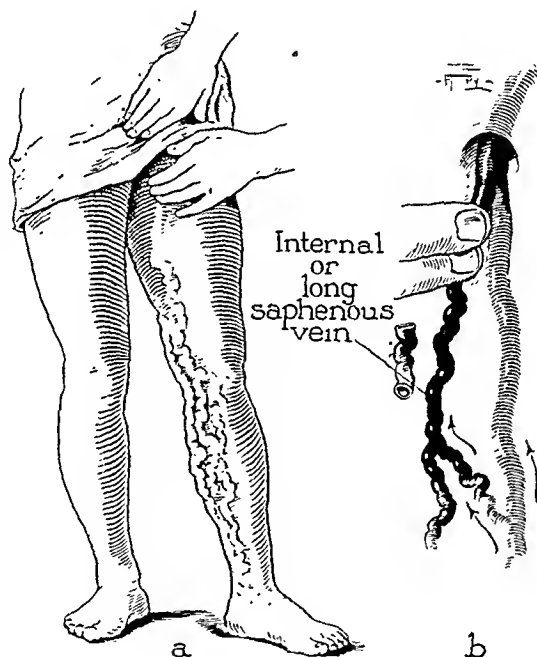


Fig. 1.—Drawings illustrating a doubly positive reaction to the Trendelenburg test. Although the examiner's fingers still compress the upper end of the long saphenous vein, the varicosities become engorged quickly (in less than thirty-five seconds) by retrograde flow through the communicating veins with incompetent valves (b) (from Ochsner, A.: *Diseases of the Veins*, in Lewis, Dean, and others: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12).

tem. The patient is instructed to walk. If the superficial venous system becomes less prominent under these conditions than when the patient walks without a tourniquet, it indicates that ligation would interfere with retrograde flow of blood through the long saphenous vein and that the patient would be benefited by ligation.

3. *Test for Competency of Deep Veins*.—A bandage, from 3 to 4 inches (7 to 10 cm.) in width, is applied like a puttee to the leg, suffi-

ciently tight to collapse the superficial veins. The patient walks up and down a room or hall for thirty minutes (fig. 2). Freedom from cramp during this period indicates free return of blood through deep veins. Sharp cramps indicate acute passive congestion due to blood which can return neither through the superficial veins because of compression nor through the deep vein because of a preexisting pathologic condition, e. g., an occlusion due to thrombophlebitis. The execution of this test is more difficult than that of the others. The bandage should be sufficiently tight to compress the superficial veins. However, if it is tight enough to compress the muscles also the compression of the muscles in itself

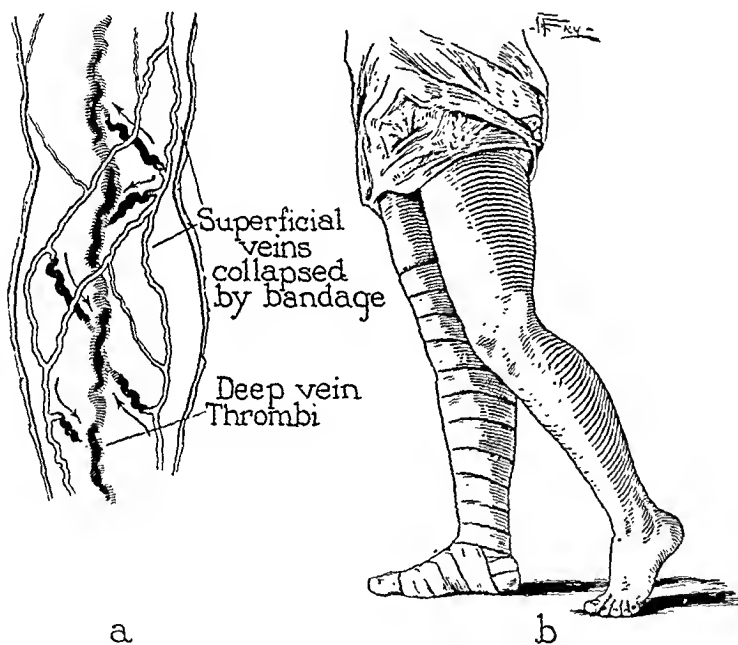


Fig. 2.—Drawings illustrating a test to determine the competency of deep veins. A firm bandage is applied to the leg from the foot to the lower part of the thigh in order to obliterate all superficial veins. The patient walks for thirty minutes. Cramping and discomfort indicate obstruction of the deep veins or of the communicating veins between the deep and the superficial system or of both (from Ochsner, A.: *Diseases of the Veins*, in Lewis, Dean: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12).

interferes with circulation and thus causes cramps and leads to a false interpretation. The test fulfils a need met by none of the other tests. Theoretically it can detect a localized, segmental obstruction in deep veins below the knee, which might not be demonstrated by the Perthes test. In cases, however, in which there is obstruction of the deep veins of the thigh compression of the long saphenous vein in the thigh by a tourniquet (Perthes' test) demonstrates the obstruction by increasing

the size of the superficial veins below. In these cases the Perthes test gives the same information as the test described in this paragraph, for the superficial veins do not collapse when the superficial circulation is obstructed in the thigh by a tourniquet and the patient is walking if the deep veins do not drain the superficial system. The one exception to the rule that the information furnished by the Perthes test is given by this test is in instances in which obstruction of the deep circulation necessitates shunting of the blood through the superficial circulation but the blood returns to a patent deep circulation below the level of the tourniquet (fig. 3).

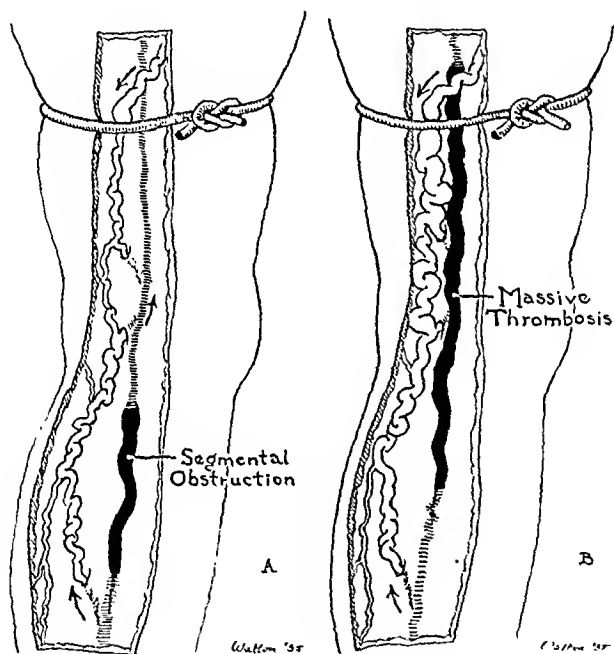


Fig. 3.—Diagrammatic representation of segmental obstruction of the deep veins of the calf. On walking with the tourniquet applied to the thigh (Perthes' test), varicosities below the tourniquet become less prominent because the blood is shunted from the deep system below the obstruction into the superficial system and back into the deep system below the tourniquet. (B) Diagrammatic representation of massive thrombosis of the deep veins. In this condition the blood from the extremity can return only through the superficial system and not through the deep veins below the tourniquet, and therefore the superficial system becomes more engorged than when the tourniquet is not applied. In an instance of this condition the Perthes test discloses the obstruction to the deep venous system as well as the test illustrated in figure 2, in contrast to the results in instances of segmental obstruction of the deep veins (A). On walking, the varicosities below the tourniquet become more prominent.

The most frequent cause of thrombosis of the deep veins of the lower extremity is pelvic infection, and in instances of such thrombosis the

femoral veins are principally involved. In relatively exceptional cases, however, thrombosis of the deep veins of the leg without concomitant involvement of the deep veins of the thigh occurs, and in such instances the test described here is of value because obliteration of the dilated superficial veins of the leg is ruled out.

*Our Test.*—We devised this test in the Tulane University surgical clinic: The patient disrobes sufficiently to show the thighs and legs. The degree of prominence of the varicose veins on standing is noted by the observer. It is essential to have a good light placed behind the sitting observer and directed toward the area of the room immediately in front of him. It is also important for the observer to sit on a low chair or stool so that his horizontal plane of vision is not much higher than the hips of the patient, permitting good views of the lower extremities. The patient then walks to and fro in front of the observer, who carefully notes any changes in the size of the veins as compared with their size in the standing position. Usually as the patient walks the veins become less prominent, owing to efficient pumping action by the muscles on the deep veins (fig. 4 *a*). After the patient has passed in review several times in this fashion, a tourniquet of thin rubber tubing is tied around the upper third of the thigh, sufficiently tight to compress the superficial veins (fig. 4 *b*). The patient then walks at the same rate of speed over the same course as before, and the observer notes the relative size of the veins as compared with their size when the patient walks without the tourniquet. Usually there is marked diminution in the prominence of the varicosities, the appreciable reduction being from 50 to 75 per cent of the degree of prominence of the veins when the patient walks without a tourniquet. This reduction is due to the fact that the circulation in the superficial system at the level of the tourniquet is inhibited and blood cannot flow backward from the femoral vein through the long saphenous vein past this level. The action of the muscles on the deep veins in walking pumps the blood more efficiently toward the heart and, in reality, milks the superficial system free from its contents below the tourniquet, and the veins become less prominent on the surface. The patient stops walking, and the tourniquet is removed and reapplied in the middle third of the thigh (fig. 4 *c*), again sufficiently tight to obstruct the flow of blood in the superficial veins. The patient again walks, and the prominence of the veins in the leg is compared with their appearance when the patient walks without the tourniquet and with the tourniquet applied around the upper third of the thigh. Similarly, the patient walks with the tourniquet around the lower third of the thigh (fig. 4 *d*). Frequently one observes that when the improvement in appearance is only moderate with the tourniquet around the upper third of the thigh, it

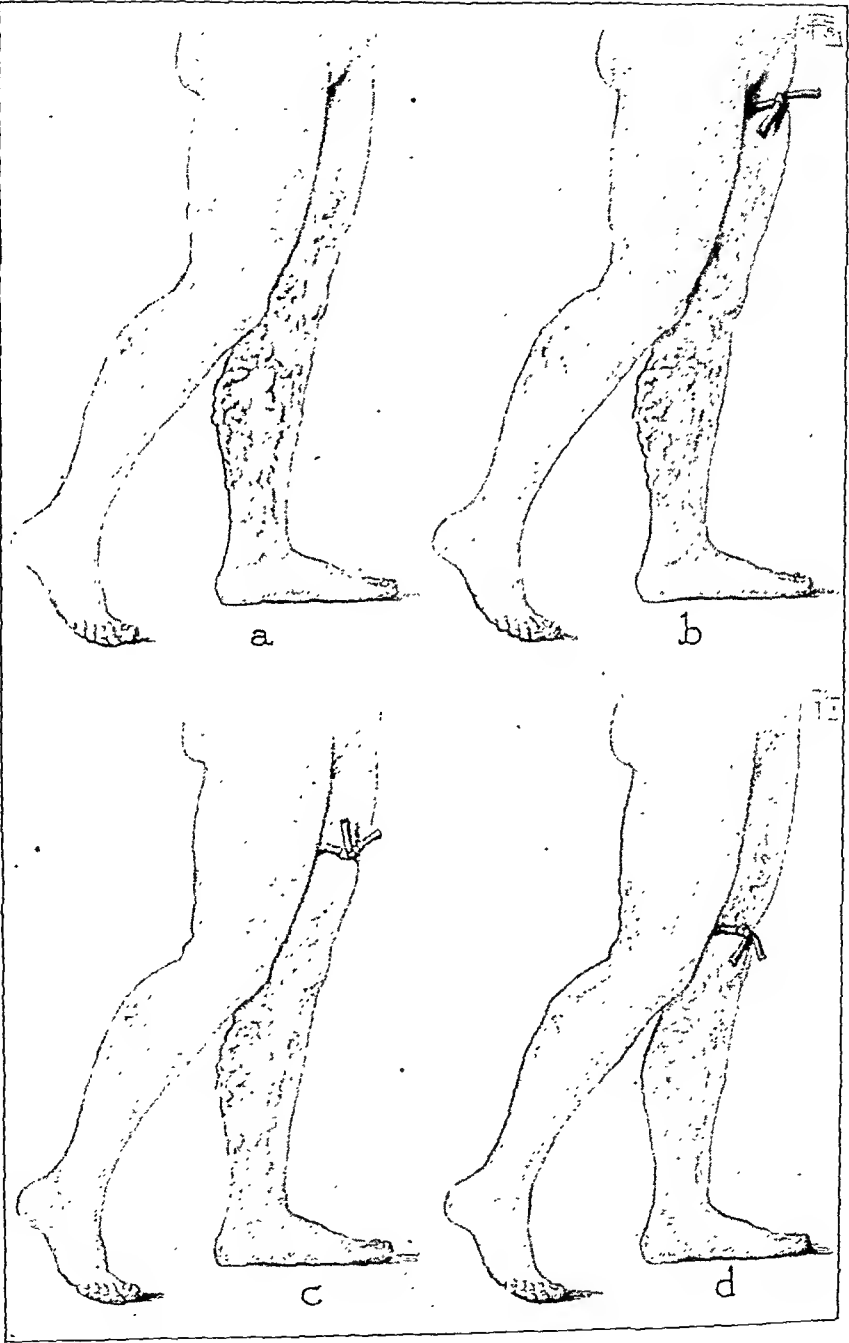


Figure 4

## EXPLANATION OF FIGURE 4

Fig. 4.—Drawings illustrating the tourniquet test for determining the competency of the valves of the communicating veins between the deep and the superficial system of the thigh. The patient walks at a normal gait, and the prominence of the veins of the calf is noted (*a*). Thereafter the tourniquet is applied to the upper third of the thigh (*b*), sufficiently tight to compress the superficial veins. Observations are made for changes in the appearance of the veins of the calf. At other times the tourniquet is similarly applied to the middle and the lower third of the thigh (*c* and *d*). The patient walks over the same course, and the prominence of the veins is noted. If the valves of all the deep communicating veins of the thigh are competent and the result of the Trendelenburg test is positive there is diminished prominence of the veins of the calf when the patient walks with the tourniquet around the upper third of the thigh. If the valves of the communicating veins are incompetent there is little or no change because the blood spills through the incompetent communicating veins from the femoral to the long saphenous vein. When the tourniquet is below the lowest communicating vein of the thigh in which the valves are incompetent (*d*) the veins of the calf become less prominent. In this instance high ligation alone is not sufficient, and low ligation also must be performed to prevent retrograde flow through communicating veins. In *b* slight improvement is shown over that indicated in *a*, in a case in which the blood spills through the communicating veins below the level of the tourniquet. In *c* slight improvement (diminution in prominence) in the veins of the calf is shown, and in *d* the greatest improvement appears. If the improvement shown in *b* were as great as that illustrated in *d* the test would indicate competency of the communicating veins of the thigh.



is marked when the tourniquet is around the lower third. Thus, the veins of the leg are observed with the patient under five conditions: (1) standing still, (2) walking without the tourniquet, (3) walking with the tourniquet applied around the upper third of the thigh, (4) walking with the tourniquet around the middle third of the thigh and (5) walking with the tourniquet around the lower third of the thigh.

#### RESULTS OF THE COMPARATIVE TEST

In some instances the veins appear less prominent with the tourniquet on the lower third of the thigh than under any of the other conditions; in other cases there is as much improvement from application of the tourniquet in the upper third of the leg as in the lower third. If the reaction to the Trendelenburg test is positive and the deep veins are not obstructed the varicose veins are less prominent when the patient walks than when he stands still, and they are even less prominent when the tourniquet is applied at each of the three levels of the leg. Usually when the tourniquet is around the lower third of the thigh the varicosities are less prominent than under any other of the five conditions. This is diagrammatically represented in figure 4 *a, b, c* and *d*, drawn from the appearance in an actual case. As shown in the drawings, the greatest improvement occurred when the tourniquet was around the lower third of the thigh.

In general, this test may have three results: (1) A frequent observation (40 per cent of the instances) is that improvement is greatest when the patient walks with the tourniquet around the lower third of the thigh and less when the tourniquet is around the middle or the upper third of the thigh but that even then it is more marked than when the patient is walking without the tourniquet; (2) the most frequent finding is that there is no difference in the size of the veins when the tourniquet is in any one of the three positions and that yet there is definitely more improvement when the tourniquet is around the thigh than when it is not, and (3) the least frequent finding is that there is no improvement with the tourniquet or that the veins are more prominent when the tourniquet is around the thigh than when it is not.

#### INTERPRETATION OF THE COMPARATIVE TEST

In instances in which the greatest improvement is seen when the tourniquet is around the lower third of the thigh, some variable must account for the fact that the improvement is greater under this condition than when the tourniquet is around the upper third of the thigh. This further improvement indicates not only that the retrograde flow through the saphenous vein comes through the main opening into the femoral vein but that there is a backward flow below the highest application

of the tourniquet which is caught when the tourniquet is moved lower. This backward flow is undoubtedly through incompetent communicating veins between the superficial and the deep system of the thigh. This is diagrammatically shown in figure 5. In the first instance, illustrated in figure 5 *d*, the tourniquet is placed above the incompetent communicating vein, and the superficial veins of the calf are still distended because the blood spills through the communicating vein to fill the veins of the calf. In figure 5 *c* the tourniquet is shown below the incompetent communicating vein, and the veins of the calf are collapsed. In this case the blood in the superficial system drains into the deep system below the tourniquet, which drainage is facilitated by the pumping action

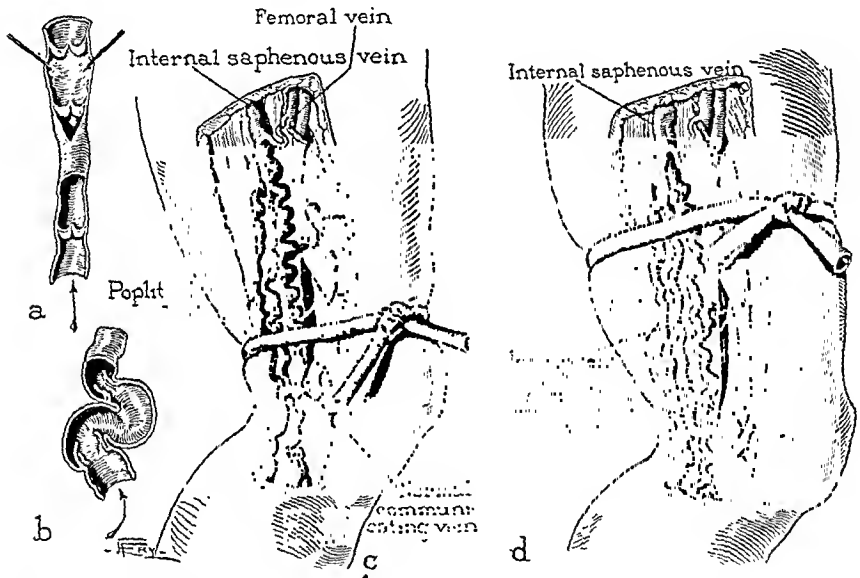


Fig. 5.—Diagrammatic representation of the mechanism involved in our test for determining the competency of the valves of the communicating veins between the superficial and the deep system of the thigh. The valves of the communicating veins above the tourniquet are incompetent (*b*) and those below are competent (*a*), thus not permitting the blood to flow from the femoral to the internal saphenous vein below the tourniquet. When the patient walks with the tourniquet as in *c*, the prominence of the veins of the calf diminishes. As compared with the positions shown in figure 5 *a*, *b* and *c*, *d* illustrates the tourniquet above the communicating veins with incompetent valves. The blood spills from the femoral vein into the internal saphenous vein through the communicating veins, and when the patient walks the change in the appearance of the veins of the calf is not as pronounced as when the tourniquet is below the communicating veins with incompetent valves, as explained in the text.

of the muscles on the deep veins, and the blood can no longer spill from above through the saphenous vein into the superficial veins of the calf.

In the instance in which there is improvement on walking with the tourniquet placed around the thigh but no difference in the degree of improvement whether the tourniquet is high or low, the following conditions are indicated: The valves of the internal saphenous vein are incompetent and there is spillage of blood from the femoral vein through the main opening of the saphenous vein, but the valves of the veins communicating between the saphenous and the femoral vein below the highest level of the tourniquet are competent and there is no retrograde flow at this point from the deep to the superficial system.

Greater prominence of the veins with the tourniquet in place indicates that in spite of the varicosities the blood can return cephalad through the superficial system only and that there is a block in the deep veins or in the veins communicating between the superficial and the deep system. In this instance the varicosities are sometimes spoken of as compensatory, and ligation or obstruction of the superficial veins is contraindicated.

#### SIGNIFICANCE OF THE TEST

It seems that if there is incompetence not only of the valves of the long saphenous vein but of those of the communicating veins between the long saphenous and the femoral vein, the lower the ligation<sup>7</sup> in the thigh the more improvement in the condition can be expected in the veins of the calf. This is true as far as temporary improvement is concerned; i. e., low ligation in many cases gives the best immediate results, but one cannot ignore the careful observation of such workers in this field as Homans,<sup>8</sup> de Takáts,<sup>9</sup> de Takáts and Quillin,<sup>10</sup> Faxon<sup>11</sup> and Edwards,<sup>12</sup> who emphasized that to avoid recurrence one must interrupt the saphenous vein above its tributaries just before it enters the

7. By ligation we do not mean that ligation alone is our method of treatment. We always use injection in conjunction with ligation in the cases in which we elect to ligate the saphenous vein. Moreover, sometimes we ligate veins other than the main stem of the saphenous vein. The present discussion is limited to indications arising from the test. Ligation means section and ligation of the distal and proximal segments.

8. Homans, J.: *The Operative Treatment of Varicose Veins, Varicose Ulcers, and Phlebitis*, New England J. Med. **200**:965, 1929; footnote 6.

9. de Takáts, G.: *Ambulatory Ligation of the Saphenous Vein*, J. A. M. A. **94**:1194 (April 19) 1930.

10. De Takáts, G., and Quillin, L.: *Ligation of the Saphenous Vein: A Report on Two Hundred Ambulatory Operations*, Arch. Surg. **26**:72 (Jan.) 1933.

11. Faxon, H. H.: *Treatment of Varicosities: Preliminary High Ligation of the Internal Saphenous Vein with the Injection of Sclerosing Solutions*, Arch. Surg. **29**:794 (Nov.) 1934.

12. Edwards, E. A.: *The Treatment of Varicose Veins*, Surg., Gynec. & Obst. **59**:916, 1934.

femoral vein. This has been our experience. Moreover, low ligation does not cure the varicosities in the saphenous stem above the level of the ligation. As a matter of fact, low ligation is followed by improvement in the varicose condition not only below but above the level of the ligation, due perhaps to the fact that there is less circulation through the vein above the ligation. We have seen this in a number of clinical cases in which we ligated the long saphenous vein low in the thigh as a first step in the treatment. The fact remains, however, that varicosities tend to recur. Collaterals which are extremely small at the time of ligation may become more active and enlarge and in time become noteworthy stems assuming the function of the saphenous vein that has been tied off. They too may become incompetent. If these collaterals are superficial veins between the proximal and the distal portion of the long saphenous vein one can obviate their incompetence by ligating the internal saphenous vein above all its tributaries. But if in the first place one ligates the saphenous vein just before it empties into the femoral vein there may be retrograde flow through communicating veins below that level, and one may not obtain the benefit of completely interrupting the retrograde flow through the saphenous vein into the veins of the calf. Injection of sclerosing solutions into the distal segment at the time of high ligation may partially or completely prevent this retrograde flow through the communicating veins, but this, too, has its uncertainties. It is not feasible to ligate each communicating stem, even though such a procedure has been advocated by authorities in this field. Search for incompetent communicating stems converts the operation into a major procedure, assuming the proportions of complete extirpation of the internal saphenous vein, and it is unnecessary here to consider the reasons why the last-mentioned operation has been discarded. In the instances in which our test shows the greatest improvement when the tourniquet is around the lowest third of the thigh, we now ligate high to prevent recurrence, inject sclerosing solution into the distal segment at the time of ligation and subsequently ligate lower to obtain the benefit of complete interruption of the flow in the long saphenous vein, even of that through incompetent communicating veins below the main opening of the saphenous into the femoral vein.

There are two observations concerning the value of which we are convinced: (1) If the test we describe shows that the communicating veins between the superficial and the deep system are markedly incompetent and high ligation is made, the patient is somewhat benefited, but little more than if a sclerosing solution were injected into the veins of the calf without ligation, and (2) in instances in which this condition exists low ligation gives by far the greatest immediate improvement. Because, as many authorities maintain, fewer recurrences through col-

lateral veins follow high ligation, in addition to this procedure low ligation may be made for optimum effect and to prevent recurrence through communicating veins.

#### SUMMARY

A new test is described for determining the direction of flow of blood in the venous system of the lower extremity affected by varicosities and for determining the competency of the valves of the long saphenous vein and communicating veins between the superficial and the deep systems of the thigh. The test gives valuable information concerning the best type of therapy and the possibilities of recurrence.

# THE PROBLEM OF WOUND HEALING

## I. EFFECT OF LOCAL AGENTS

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PHILADELPHIA

The surgical literature contains reports of the use of numerous topical substances purported to stimulate wound healing. It is my purpose in this article to consider the problem of their evaluation and to present the results obtained in a critical study of certain agents frequently used as wound dressings.

### HISTORICAL SURVEY

The Edwin Smith Surgical Papyrus, the first written record in medical history and perhaps the earliest exegesis of the scientific method in human history, contains a discussion of the principles to be followed in the management of traumatic wounds. During the centuries, knowledge has accrued concerning both the mechanisms of repair and the therapeutics of wounds; yet today these subjects remain in the forefront of surgical thought as problems lacking final solution. The fact that surgeons have yet to attain perfection in the treatment of wounds apparently has constituted a challenge to investigators, judging from the multiplicity of substances brought forward to speed up repair. In evaluating these agents one must consider the processes of wound healing, since in the last analysis any substance of worth in wound therapy must act on these functions.

Recognition of the grosser phenomena relating to tissue repair occurred at an early date. The writings of Hippocrates reveal that the Greeks had already distinguished between primary and secondary healing, and Celsus in the first century A. D. attempted to secure the former through the use of sutures, control of bleeding and prevention of pus formation. These measures were discarded during the Middle Ages, with the acceptance of the antithetic Arabian creed that wounds must suppurate to heal. It remained for the surgical leaders of the Renaissance, Hugh of Luccia, Henri de Mondeville and Theodoricus, to restore the concept that healing per primam intentionem is normal and desirable. By the sixteenth century there developed a conflict which remains

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From the Harrison Department of Surgical Research, University of Pennsylvania, and the Surgical Clinic of the Hospital of the University of Pennsylvania.

unsettled to this day. Paré and Paracelsus attributed healing to the inherent forces of nature rather than to the efforts of the surgeon and contended that it is the surgeon's prime duty to permit these forces to act with a minimum of interference. In an opposite school of thought the attitude prevailed that adequate treatment of a wound demands relentless anointment with one vulnerary after another, in order to achieve a maximum rate of healing.

Understanding of the histologic phenomena of repair followed the discovery of the microscope, the enunciation of the cell doctrine and the introduction of the technic for preparing microscopic sections. After Virchow had built his cellular pathology, repair came to be expressed in terms of cellular and vascular reactions. Observation of living tissues by von Recklinghausen and Cohnheim and studies of cultures *in vitro* clarified the interrelationships among the several cell types—vascular elements, fixed tissue cells and mobile tissue cells—which enter into wound healing.

Concomitantly the influence of bacterial agents on the reparative functions was elucidated. From these developments, which are largely contributions of the past half-century, there has come the present concept of the histology of inflammation and repair, a concept which with respect to its broad outline enjoys general acceptance.

The standard surgical textbooks divide the reactions of the tissue in a traumatic wound into an exudative and a reparative phase. Any irritant destructive of tissue invokes vascular changes and an exudative response of leukocytic and mobile tissue cells and of antibody constituents of the serum, which collectively localize and minimize the effects of the irritant. Reparative phenomena then follow; in surface wounds these consist of capillary budding, fibroblastic proliferation and epithelial ingrowth, all so regulated as ultimately to restore the continuity of the tissue. Harvey<sup>1</sup> has well summarized the events of repair in his statement: "From the view-point of the surgeon, then, the healing of a wound is largely a function of the covering epithelium and certain fibroblastic elements derived from mesenchyme . . ."

While the essential features of the structural mechanism of repair have been established, the underlying forces which motivate the process remain to a large degree obscure. What are the factors consequent on trauma which cause adult cells to resume embryonal proliferative characteristics? After many studies on tissues *in vitro* Carrel<sup>2</sup> concluded that "healing is not initiated by traumatism or the loss of tissues, but by substances resulting directly or indirectly from the traumatism." He expressed the belief that these growth-promoting substances are protein

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1. Harvey, S. C.: *Proc. Inst. Med. Chicago* 10:70, 1934.

2. Carrel, A.: *Proc. Inst. Med. Chicago* 8:62, 1930.

and that they are liberated either by the breakdown of the tissue itself or by the manufacturing activity of leukocytes, particularly lymphocytes, on cellular débris and the constituents of serum. Fisher<sup>3</sup> resected a triangular segment from a slowly growing culture of fibroblasts and observed a renewal of growth throughout the colony. Subsequent to experiments on plants and animals, Hammett and Reimann<sup>4</sup> advanced the hypothesis that the "sulphydryl group is the wound hormone or essential chemical factor in the cell proliferation following trauma." Whatever the chemical agent which initiates the reparative functions, the more recent tendency has been to seek such a substance rather than to follow the older belief of Virchow that trauma per se activates the cells involved in healing.

No attempt has been made to review all the contributions dealing with the responses of the tissue to injury. Rather I have sought to survey briefly the present knowledge of the processes of repair, because from the point of view of therapeutics a consideration of these processes must serve as a background for the evaluation of the effect of any purported vulnerary. The immediate question confronting the surgeon is whether or not means are available to act on the reparative mechanism in a stimulating manner. Without consideration of forces inherent in a wound it is apparent that the rate of healing may be affected by factors localized directly at the site of the wound and by factors of a more general nature present or administered at a distance.

Variables which may influence healing from a distance are (1) diet, (2) hormones and (3) infection existing elsewhere in the body. From measurements of surface wounds in dogs Clark<sup>5</sup> found that as compared with diets high in carbohydrates and mixed diets, those high in protein shortened the period of latency before healing commenced and those high in fat lengthened it, but that subsequent to its onset repair was not influenced by the diet. On the other hand, observations by Harvey and his colleagues<sup>6</sup> on increasing increments in the tensile strength of gastric incision wounds indicated that diet did not affect the duration of the period of latency but that a diet with a high protein content resulted in more rapid attainment of maximum strength. It was further noted that starvation effected no change either in the rate of incidence of fibroplasia or in its velocity. As a result of these studies Harvey<sup>1</sup> concluded that "the normal animal when subjected to a wound

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3. Fisher, A.: Tissue Culture, Copenhagen, Levin & Munksgaard, 1925.

4. Reimann, S. P.: Proliferation of Rat and Mouse Epithelium from Sulphydryl, *Protoplasma* **10**:82 (June) 1930.

5. Clark, A. H.: *Bull. Johns Hopkins Hosp.* **30**:117, 1919.

6. Harvey, S. C., and Howes, E. L.: *Ann. Surg.* **91**:641, 1930.



will repair this without respect to the character of diet or even lack of food . . .” With regard to accessory food factors, investigation has largely centered about vitamin A. Lohr<sup>7</sup> and Continental observers have stressed the beneficial influence of cod liver oil, but Roegholt<sup>8</sup> reported that deficiency of vitamin A caused no alteration in the rate of wound healing. The belief was expressed by Bird and MacKay<sup>9</sup> that patients postoperatively should be placed on high fluid intakes, since moderate dehydration in rats comparable to states observed clinically markedly inhibited the process of repair.

The endocrine glands the functions of which have been correlated with the reparative processes are the pancreas, the thyroid gland, the adrenal glands and the gonads. Rabinowitch<sup>10</sup> cited reports of twenty cases in which the patients did not have diabetes but had a condition marked by impairment in tolerance for carbohydrates, the administration of insulin being followed by rapid closure of a previously nonhealing wound. Sullivan<sup>11</sup> obtained a similar response with postpellagrous trophic ulcers. On the basis of experimentation with animals, Kosdoba<sup>12</sup> and Ciantini<sup>13</sup> attributed to the thyroid gland and the adrenal glands a significant rôle in the regenerative processes. Wheeler and Adams<sup>14</sup> reported on a cholecystectomy incision wound which underwent retrogression at each menstrual cycle for two years and then healed shortly after bilateral ablation of the ovaries.

The clinical impression that cicatrization is retarded by the presence of remote collections of purulent material has received experimental support from the work of Carrel.<sup>15</sup> Turpentine was injected subcutaneously into dogs with surface wounds; coincident with the development of sterile abscesses healing diminished in rate or ceased, regaining its normal velocity on drainage. Subcutaneous administration of the sterile pus to other animals inhibited their reparative powers, thereby indicating that pus contains constituents inimical to healing.

It is on consideration of the many agents purported to influence the course of wound healing through local action that one enters a

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7. Lohr, W.: *Med. Welt* **8**:1273, 1934.

8. Roegholt, N.: *Nederl. tijdschr. v. geneesk.* **2**:3744, 1929.

9. Bird, C. E., and MacKay, E. M.: *Surg., Gynec. & Obst.* **54**:872, 1932.

10. Rabinowitch, I. M.: Simultaneous Respiratory Exchange and Blood Sugar Time Curves Obtained in Apparently Nondiabetic Patients with Nonhealing Wounds, *Arch. Surg.* **26**:696 (April) 1933.

11. Sullivan, E. A.: *New England J. Med.* **209**:241, 1933.

12. Kosdoba, A. S.: *Arch. f. klin. Chir.* **179**:435 and 551, 1934.

13. Ciantini, F.: *Ann. ital. di chir.* **12**:1119, 1933.

14. Wheeler, B. C., and Adams, D. S.: *New England J. Med.* **211**:630, 1934.

15. Carrel, A.: *Compt. rend. Soc. de biol.* **90**:333, 1924

moot field in surgical therapeutics. Beyond doubt a number of local factors are of significance. The degree and type of infection, the presence of foreign bodies, the trophic state of the tissues as regards blood and nerve supply, the amount of traumatism associated with dressing—all these indisputably affect the course of repair. But is there any valid basis for the claims concerning the therapeutic value of the horde of topical vulneraries, whether antiseptic or stimulant? Has the contention been substantiated that antiseptics further repair by exerting a selectively greater effect on bacteria than on the tissues? Do the supposed stimulants actually stimulate?

It would be impossible in a paper of this scope to evaluate critically or even to list the agents favorably advocated as stimulants of repair. Those based on Hammett's<sup>16</sup> work on the sulfhydryl radical include thiocresol, thioglycerol, cysteine, glutathione and insulin applied locally. Good results have been claimed for many physical agents: roentgen rays, ultraviolet rays, infra-red rays, diathermy, oxygen and carbon dioxide gas. Several investigators have employed embryonic extract and allantoic fluid, because of their admitted propensities for the stimulation of growth. Antigenic substances, such as bacterial filtrates and protein broths, as well as bacteriophages, have been used. A few hormones and vitamins have been applied locally, such as parathyroid extract, thyroid and testicular extracts, cod liver oil and viosterol. Still other advocated stimulants are peruvian balsam, irradiated petrolatum and amino-azotolueneazo-beta-naphthol, the active ingredient in scarlet red ointment. It has even been seriously proposed to treat wounds with the inner lining membrane of the hen's egg.

#### METHODS FOR EVALUATION OF STIMULANTS OF REPAIR

While certain of the purported stimulants of healing have been subjected to experimentation on animals, the evidence in behalf of the great number rests on clinical observation. The customary experimental procedure has been to prepare two bilaterally symmetrical wounds, one serving as a test object and the other as a control, and then to compare the length of the periods required for healing.

Before accepting conclusions drawn from results obtained by this technic one may well raise the following questions: 1. Will the time required for healing be precisely identical for two corresponding wounds similarly treated, and if not, what are the limits of expected variation? 2. How significant are the errors introduced by slight differences in size of the wounds and in other factors which are acting but presumably constant? 3. If the two preceding questions cannot be ruled out as

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16. Hammett, F. S.: *Protoplasma* 7:297, 1929.

inconsequential, what number of favorable observations is required to establish statistically the superiority of a particular substance under investigation?

A similar trend of thought is applicable to those studies in which results are derived from the examination of histologic sections. If one may require that inferences based on experiments with animals adequately meet the aforementioned criteria, it must be concluded that therapeutic efficacy has not been convincingly demonstrated for most of the proposed vulneraries tested by this method.

Likewise, the possibility of error has not been adequately eliminated by many reports advocating substances as stimulants of wound repair after apparently successful clinical trial. A fair number of the reports can be classified only as enthusiastic but uncontrolled impressions. For the most part, however, the conclusions drawn are founded on encouraging response of the wound to the application of a test agent, either in contrast to the effects of other materials used alternately or after a previous period of resistance to healing. It is difficult to estimate the magnitude of individual subjectivity in such observations. Furthermore, although there may occur a favorable response coincident with the institution of a particular mode of therapy, a causal relationship is not thereby established. Not only can a number of factors at a distance from a wound influence the course of its repair, as previously pointed out, but at the present time knowledge of these factors can hardly be regarded as complete. Consequently, the assumption that these forces remain constant throughout long intervals is at least doubtful, and an equal degree of doubt must extend to the conclusions dependent on such an assumption.

It is evident, then, that reliable assessment of the so-called wound stimulants requires more accurate methods of evaluation than those generally employed. The problem demands a quantitative approach. From studies of superficial, chemically sterilized wounds in man and in animals, Carrel<sup>17</sup> and his associates demonstrated wound repair to be an exponential function, with the rate at any given time governed by two intrinsic factors, the area of the wound and the age of the patient. The curves of normal wound healing presented by Carrel establish that the rate of healing is proportional to the area of the wound and decreases with the age of the patient. Du Noüy<sup>18</sup> expressed mathematically the interrelationships among these elements; his formula permits the prediction of the period in which a wound should normally heal and the calculation of the expected area of the wound at any time during the

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17. Carrel, A., and Hartmann, A.: *J. Exper. Med.* **24**:429, 1916.

18. Du Noüy, P. L.: *J. Exper. Med.* **24**:461 (Nov.) 1916.

course of repair. In his article on acute empyema Heuer<sup>19</sup> stated: "Foulger has repeatedly predicted the date of healing of empyemic cavities from this formula and with a fair degree of accuracy." The work of Carrel and Du Noüy published in 1910 constitutes practically the only quantitative contribution to the problem of wound repair in man.

It is my belief that the existing controversy as to the place of topical agents in the treatment of wounds has resulted from the failure to apply quantitative considerations in the determination of their worth. Consequently, I adopted the following procedure in order to ascertain on the basis of precise measurement the clinical effects of a selected list of dressings.

My investigation was carried out on a series of sixteen patients, all in good general health unless otherwise indicated. The wounds studied differed in size and etiology, but each was of the type regarded as surgically clean. Each wound was dressed with two or more of the substances under investigation during alternate periods of varying duration. Under these conditions I have followed the course of healing, taking measurements of changes both in area and in volume at frequent intervals.

The area was obtained by placing a small celluloid film directly on the wound and tracing the line of union between the epithelial edge and the granulating surface. This tracing was then transferred to a sheet of paper, and the area was determined with a planimeter. Volume was determined by pouring a mold with sterilizable material which assumed the exact configuration of the granulating tissue and the surface of which could be trimmed to conform to the contour of the body. Cultures were taken from time to time to follow the bacteriologic status of the wound. From the data thus collected I plotted for each wound studied a curve representing the course of its healing under the successive local dressings.

The data were then evaluated on the following basis:

The broken line in chart 1 indicates the observed rate of healing of a wound when materials *A* and *B* were applied during alternate periods of the designated length. It is apparent that the curve of repair for this hypothetical wound is not geometric in form, but it is possible to draw a smooth curve showing the average rate of healing throughout the entire period of cicatrization. The solid line (chart 1) represents what I have arbitrarily considered to be the average rate of healing. For any single period it is possible to compare the slope of the broken line showing the actual rate of healing during that period with the

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19. Heuer, in Graham, E. A.; Singer, J. J., and Ballon, H. C.: *Surgical Diseases of the Chest*, Philadelphia, Lea & Febiger, 1935.

curve indicating the average rate of healing. In this way I have classified healing during each period of observation as accelerated, average or retarded. Clearly this method evaluates the two substances applied only in terms of each other; it affords no comparison between the observed rate of healing and a theoretically normal rate. I may say, however, that any agent which is truly a stimulant will consistently increase the velocity of healing as compared with the average rate under the existing conditions. Furthermore, Carrel's<sup>17</sup> work on the velocity of normal repair has demonstrated that the slope of the curve at the onset of healing tends to be vertical, then becomes progressively less steep and ultimately approaches the horizontal. Therefore, the action

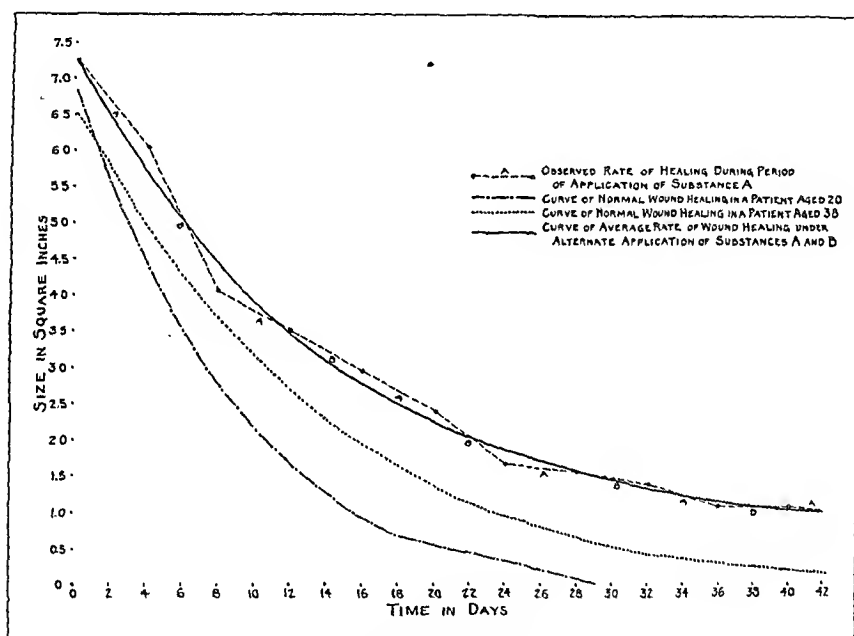


Chart 1.—Curves of wound healing.

of a stimulant should be most readily discernible in the later stages of wound healing, when one may expect the curve of repair to assume a horizontal direction.

The following practices were adopted in order to control to the greatest possible degree the influence of extraneous factors on the results obtained. In each patient studied an effort was made to maintain the diet and the intake of water at an approximately constant level, and the state of general health was carefully checked from time to time. So far as the time required for healing permitted, the agents tested on any particular wound were repeatedly applied, so that favorable and unfavorable influences exerted by nonlocal forces might mutually compensate. Two patients had multiple wounds, allowing comparison of

the effects obtained by simultaneous treatment with different modes of dressing. The majority of substances reported on were applied to the wounds of five or more patients, the final evaluations being based on the composite results.

The substances which have been studied by the technic outlined may be divided into three groups:

1. Admittedly inert agents: Petrolatum gauze, physiologic solution of sodium chloride and dry gauze dressing.

2. Antiseptic agents: 1:1,000 solution of merthiolate, 1:2,000 merthiolate ointment, 4 per cent solution of mercurochrome, zinc perox-

TABLE 1.—*Wound Resulting in G. H. from Removal for Biopsy of Acutely Inflamed Lymph Nodes (Right Inguinal Region)*

Date	Dressing	Period of Application, Days	Volume of Wound, Cc.			Rate of Healing
			Start	End	Change	
9/1 to 9/3	Dry packing and dressing...	2	9.6	9.6	0	Retarded
9/3 to 9/5	Dry packing and dressing...	2	9.6	9.1	0.5	Average
9/5 to 9/7	Dry packing and dressing...	2	9.1	7.5	1.6	Accelerated
9/1 to 9/7	Summary of period with dry dressing.....	6	9.6	7.5	2.1	
9/7 to 9/10	Wet merthiolate.....	3	7.5	6.7	0.8	Average
9/10 to 9/12	Wet merthiolate.....	2	6.7	6.6	0.1	Retarded
9/12 to 9/14	Wet merthiolate.....	2	6.6	6.1	0.5	Average
9/7 to 9/14	Summary of period with wet merthiolate.....	7	7.5	6.1	1.4	
9/14 to 9/17	Dry dressing.....	3	6.1	6.1	0	Retarded
9/17 to 9/19	Wet merthiolate.....	2	6.1	4.7	1.4	Accelerated
9/19 to 9/21	"	2	4.7	4.9	-0.2	Retarded
9/21 to 9/24	"	3	4.9	4.0	0.9	Accelerated
9/24 to 9/27	"	3	4.0	2.6	1.4	Accelerated
9/27 to 10/1	"	4	2.6	3.2	-0.6	Retarded
10/1 to 10/4	Dry dressing.....	3	3.2	2.4	0.8	Average
10/4 to 10/8	Wet merthiolate.....	4	2.4	1.7	0.7	Average
10/8 to 10/11	Wet sodium chloride.....	3	1.7	1.0	0.7	Average
10/11 to 10/15	Wet merthiolate.....	4	1.0	0.4*	0.6	Average

\* Granulations filled in to maximal extent and wound almost epithelialized.

ide paste (consisting of zinc peroxide and water) and a paste consisting of zinc oxide, acacia and glycerin.

3. Presumably stimulating agents (some with antiseptic properties): 0.25 per cent thiocresol in solution and in ointment, irradiated petrolatum, a 0.6 per cent solution of allantoin, peruvian balsam and ultraviolet irradiation.

Among these substances major attention was devoted to merthiolate, mercurochrome, thiocresol, petrolatum gauze, solution of sodium chloride and dry gauze dressing.

#### OBSERVATION ON CASES

The following cases are typical of the entire series investigated:

CASE 1.—G. H., a man aged 32, had a wound resulting from excision for biopsy of a mass of inflamed lymph nodes in the right inguinal region. Through-

out the course of healing the wound showed healthy pink granulation tissue and was practically free from purulent discharge despite a positive culture of *Staphylococcus aureus-haemolyticus* and diphtheroid bacilli. During alternate periods of from two to seven days dressings of a 1:1,000 solution of merthiolate and dry gauze were applied, and the influence on the volume of the wound was measured.

The curve of healing (chart 2) reveals that neither dressing exerted a consistent effect on the velocity of repair. During the first six days, when dry gauze was used, the rate of healing as compared with the average rate was retarded for the first two days, average for the next two and accelerated for the last two. For the next seven days a solution of merthiolate was applied, and the rate of healing during that time was, in succession, average, retarded and average. During all the periods of observation in which dry dressing was employed, the rate of healing was average twice, accelerated twice and retarded three

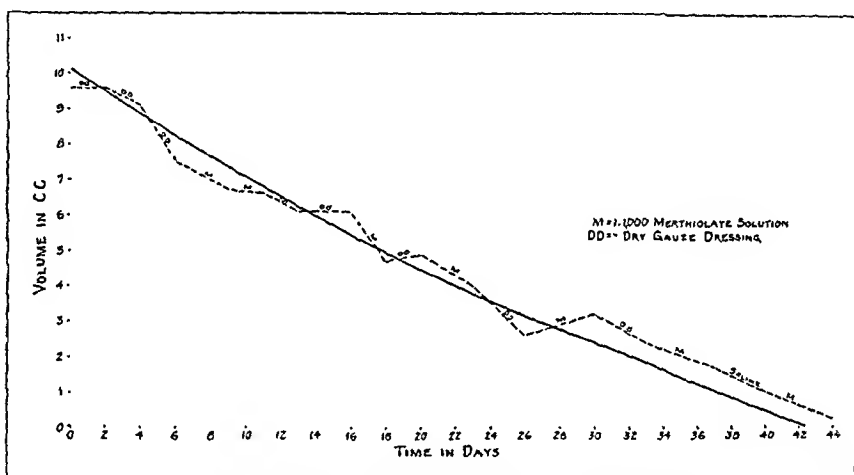


Chart 2 (case 1).—Curve of healing of biopsy wound of inguinal lymph nodes.

times. When merthiolate was employed, the rate of healing was average four times, accelerated twice and retarded twice.

CASE 2.—W. J., a youth of 18 (table 2), as a result of plastic surgical procedures requiring multiple skin grafting, presented on one occasion shallow ulcers which had appeared simultaneously on the hand and the abdominal wall and a somewhat larger ulcer which had appeared at a later date on the hip. The former two ulcers were treated with merthiolate ointment, petrolatum gauze and dry dressing. To the latter ulcer only merthiolate ointment was applied. Progressive changes in the area of the wound were measured. The three ulcers presented vascular granulation tissue and were almost free from secretion.

Until the ulcer on the hand healed, it and the abdominal ulcer were similarly treated. The curve (chart 3) of repair for the ulcer on the hand was entirely geometric in form, notwithstanding treatment with merthiolate ointment, dry dressing and petrolatum gauze. During the corresponding period the curve for the identically dressed abdominal ulcer did not run parallel, but in the later stages of healing it became almost a straight line, despite alternate application of petrolatum gauze, merthiolate ointment and dry dressing. These observations suggest that factors other than the topical dressing governed the course of

TABLE 2.—Effect of Dressings on Abdominal Ulcer Resulting from Removal of a Skin Graft, an Ulcer of the Hand Resulting from Partial Necrosis of a Skin Graft and an Ulcer of the Hip Resulting from Removal of a Skin Graft

Date	Mode of Dressing	Period of Application, Days	Area of Abdominal Ulcer, Sq. In.			Area of Hand Ulcer, Sq. In.			Area of Hip Ulcer, Sq. In.		
			Start	End	Change	Start	End	Change	Start	End	Change
12/10 to 12/17	Merthiolate ointment	7	0.75	0.47	0.28	0.38	0.12	0.26			
12/17 to 12/24	Dry dressing	7	0.47	0.64	-0.17	0.12	0.12	0.00			
12/24 to 12/31	Merthiolate ointment	7	0.64	0.22	0.42	0.12	0.05	0.07			
12/31 to 1/7	Petrolatum gauze	7	0.22	0.25	-0.03	0.05	0.03	0.02			
1/7 to 1/14	Merthiolate ointment	7	0.25	0.26	-0.01	0.03	0.00	0.03			
1/14 to 1/21	Dry dressing	7	0.26	0.22	0.04	....	....	....			
1/21 to 1/28	Merthiolate ointment	7	0.22	0.11	0.11	....	....	....			
4/22 to 4/24	Merthiolate ointment	2	....	....	....	....	....	....	1.81	2.04	-0.23
4/24 to 4/27	Merthiolate ointment	3	....	....	....	....	....	....	2.04	1.74	0.30
4/27 to 4/30	Merthiolate ointment	3	....	....	....	....	....	....	1.74	1.58	0.16
4/30 to 5/3	Merthiolate ointment	3	....	....	....	....	....	....	1.58	1.50	0.08
5/3 to 5/6	Merthiolate ointment	3	....	....	....	....	....	....	1.50	1.21	0.29
5/6 to 5/10	Merthiolate ointment	4	....	....	....	....	....	....	1.21	1.22	-0.01
5/10 to 5/15	Merthiolate ointment	5	....	....	....	....	....	....	1.22	1.15	0.07
5/15 to 5/18	Merthiolate ointment	3	....	....	....	....	....	....	1.15	1.05	0.10
5/18 to 5/21	Merthiolate ointment	3	....	....	....	....	....	....	1.05	1.02	0.03
5/21 to 5/28	Merthiolate ointment	7	....	....	....	....	....	....	1.02	1.44	-0.42
5/28 to 5/31	Merthiolate ointment	3	....	....	....	....	....	....	1.44	0.48	0.96
5/31 to 6/4	Merthiolate ointment	4	....	....	....	....	....	....	0.48	0.87	-0.39
6/4 to 6/8	Merthiolate ointment	4	....	....	....	....	....	....	0.87	0.47	0.40
6/8 to 6/11	Merthiolate ointment	3	....	....	....	....	....	....	0.47	0.24	0.23
6/11 to 6/14	Merthiolate ointment	3	....	....	....	....	....	....	0.24	0.10	0.14
6/14 to 6/17	Merthiolate ointment	3	....	....	....	....	....	....	0.10	0.04	0.06
6/17 to 6/21	Merthiolate ointment	4	....	....	....	....	....	....	0.04	0.00	0.04

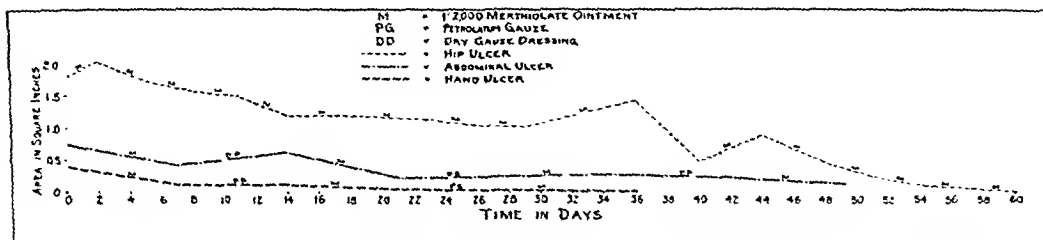


Chart 3 (case 2).—Curves of healing of ulcers on the hip, abdomen and hand, resulting from skin grafts.



repair and that the three agents employed exerted no significant effect. This point of view is further borne out by the curve of healing for the ulcer on the hip, which manifested a series of irregularities during constant treatment with merthiolate ointment.

CASE 3.—C. J., an 11 year old boy (table 3), had traumatic ulcers on the left anterior tibia and the right ankle. Throughout the course of investigation the ulcer on the tibia on repeated culture showed hemolytic streptococci and Staph. aureus; a moderate purulent discharge persisted, although at all times the granulation tissue was richly vascular and healthy in appearance. During the period of study, the patient received a high calorie, vitamin-rich diet and gained in weight, and his general health underwent no evident changes. The substances used in local treatment comprised the antiseptic, merthiolate ointment, the inert

TABLE 3.—*Effect of Dressings on Ulcers over the Anterior Aspect of the Left Tibia and the Right Ankle Resulting from Trauma*

Date	Mode of Dressing	Period of Appli- cation, Days	Area of Ulcer, Sq. In.			Rate of Healing
			Start	End	Change	
Left Anterior Tibial Ulcer						
4/29 to 5/ 1	Petrolatum gauze.....	2	2.38	2.34	0.04	Average
5/ 1 to 5/ 3	Petrolatum gauze.....	2	2.34	2.23	0.11	Average
5/ 3 to 5/ 7	Merthiolate ointment.....	4	2.23	2.63	-0.40	Retarded
5/ 7 to 5/10	Merthiolate ointment.....	3	2.63	2.30	0.33	Accelerated
5/10 to 5/13	Petrolatum gauze.....	3	2.30	2.74	-0.44	Retarded
5/13 to 5/16	Petrolatum gauze.....	3	2.74	3.46	-0.72	Retarded
5/16 to 5/21	Merthiolate ointment.....	5	3.46	4.23	-0.77	Retarded
5/21 to 5/23	Thiocresol ointment (0.25%)....	2	4.23	3.68	0.55	Accelerated
5/23 to 5/26	Allantoin solution (0.6%).....	3	3.68	1.40	2.28	Accelerated
5/26 to 5/28	Allantoin solution (0.6%).....	2	1.40	1.43	-0.03	Retarded
5/28 to 5/31	Merthiolate ointment.....	3	1.43	1.42	0.01	Retarded
5/31 to 6/ 3	Merthiolate ointment.....	3	1.42	0.79	0.63	Accelerated
6/ 3 to 6/10	Merthiolate ointment.....	7	0.79	0.87	-0.08	Retarded
6/10 to 6/13	Merthiolate ointment.....	3	0.87	1.14	-0.27	Retarded*
6/13 to 6/17	Thiocresol ointment (0.25%)....	4	1.14	0.95	0.19	Average
6/17 to 6/20	Dry dressing.....	3	0.95	0.90	0.05	Average
6/20 to 6/24	Allantoin solution.....	4	0.90	0.72	0.18	Average
6/24 to 6/27	Merthiolate ointment.....	3	0.72	0.20	0.52	Accelerated
Ulcer on Right Ankle						
5/23 to 5/26	Thiocresol ointment (0.25%)....	3	2.20	0.48	1.77	
5/26 to 5/28	Thiocresol ointment (0.25%)....	2	0.48	0.08	0.35	
5/28 to 5/31	Thiocresol ointment (0.25%)....	3	0.08	0.00	0.08	

\* Ulcer accidentally bruised.

substances, petrolatum and dry gauze, and the stimulants, thiocresol ointment and allantoin solution. Measurement was made of the area of the wound.

Because of the irregular progress of healing in the tibial ulcer it is difficult to evaluate slight degrees of acceleration or retardation in the velocity of repair (chart 4); yet certain facts are definite. No single agent applied was constant in its action. The one marked "spike" in the course of healing occurred under local dressings, which at other times clearly exerted neither such deleterious effects nor favorable influence. The effects of thiocresol and of allantoin on both the ulcers during the twenty-second to the twenty-seventh day appeared most propitious, but the rates of healing during the next several days and on subsequent occasions hardly justify any enthusiastic claims regarding their therapeutic value. Considered as a whole, the observations indicate that whatever effect the local dressings may have produced on the velocity of repair, their action was inconstant and was probably overbalanced by other factors.

CASE 4.—R. U., a woman of 31, subsequent to incision and drainage of abscesses in her thigh presented three wounds, placed anteriorly, medially and

laterally. There was originally a pure culture of hemolytic streptococci; for a time afterward these organisms and *Staph. aureus* predominated among a number of bacteria. The granulating surfaces tended to appear torpid and avascular throughout the period of observation. Secretion from the wound at first was

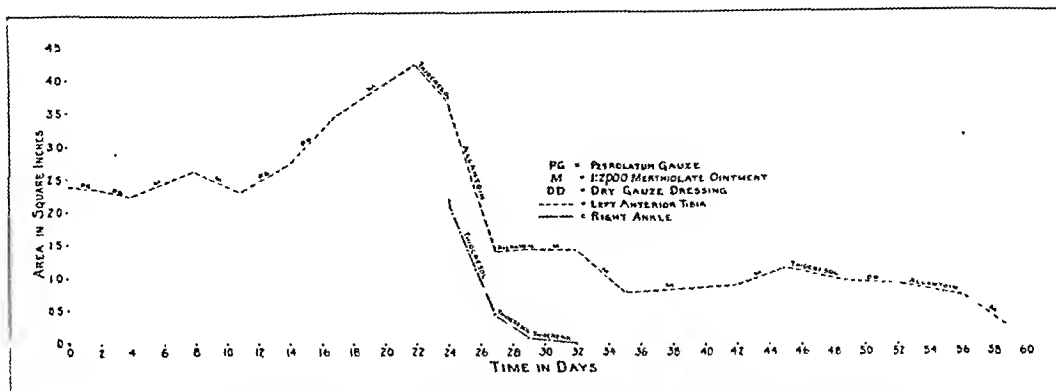


Chart 4 (case 3).—Curves of healing of ulcers of the left anterior tibia and the right ankle.

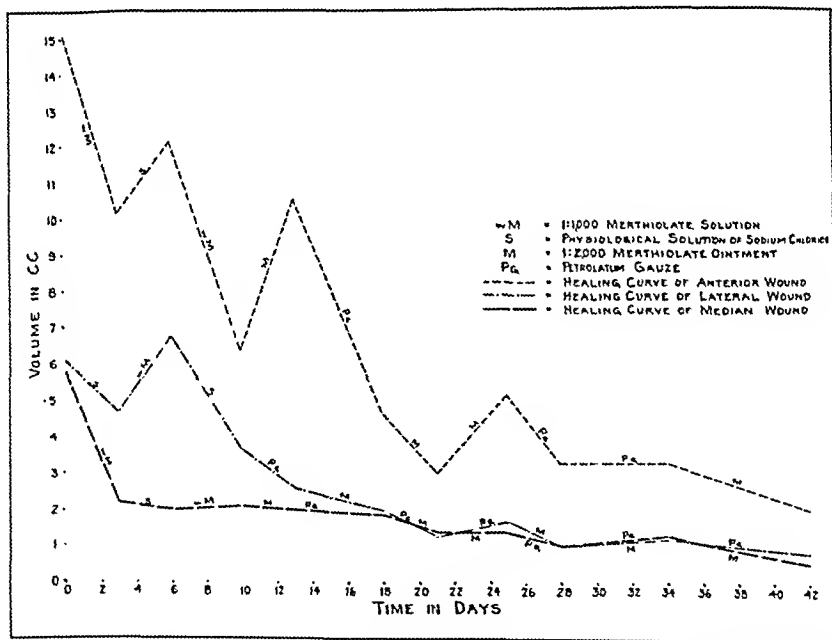


Chart 5 (case 4).—Curves of healing of incision wounds in cellulitis of the thigh.

moderate; later it diminished in quantity. To each wound, merthiolate and either physiologic solution of sodium chloride or petrolatum gauze were applied alternately. During any single period the anterior and the medial wound were dressed similarly, while the alternate dressing was used on the lateral wound.

If each curve (chart 5) is looked at separately considerable irregularity can be noted in the rate of repair, but no consistent relationship can be observed

between the dressing used and the slope assumed by the curve. When the three curves are viewed together, a trend toward parallelism can be detected. This correspondence differs in degree and is not invariable, but it is definitely present. Consideration of the individual curves suggests that healing occurred by fits and starts. The occurrence of these fits and starts simultaneously in the three

TABLE 4.—*Effect of Dressings on a Decubitus Ulcer in the Right Trochanteric Area*

Date	Mode of Dressing	Period of Application, Days	Volume of Wound, Cc.			Area of Wound, Sq. In.		
			Start	End	Change	Start	End	Change
8/11 to 8/17	Wet merthiolate.....	2	30.0	24.0	6.0	6.4	6.3	0.1
8/13 to 8/15	Dry gauze dressing.....	2	24.0	22.9	1.1	6.3	6.5	-0.2
8/15 to 8/17	Wet merthiolate.....	2	22.9	24.0	-1.1	6.5	7.5	-1.0
9/ 8 to 9/17	Dry dressing.....	9	9.5	9.0	0.5	4.9	4.6	0.3
9/17 to 9/19	Wet merthiolate.....	2	9.0	9.5	-0.5	4.6	4.7	-0.1
9/19 to 9/21	Dry dressing.....	2	9.5	8.9	0.6	4.7	4.1	0.6
9/21 to 9/24	Thiocresol 48 hours; solution of sodium chloride 24 hours.	3	8.9	6.3	2.6	4.1	3.9	0.2
9/24 to 9/26	Thiocresol.....	2	6.3	11.0	-4.7	3.9	3.6	0.3
9/21 to 9/26	Thiocresol (summary).....	5	8.9	11.0	-2.1	4.1	3.6	0.5
9/26 to 10/1	Solution of sodium chloride...	5	11.0	10.2	0.8	3.6	3.2	0.4
10/1 to 10/3	Thiocresol.....	2	10.2	8.0	2.2	3.2	3.0	0.2
10/3 to 10/9	Solution of sodium chloride...	6	8.0	3.0	5.0	3.0	3.9	-0.9*
10/9 to 10/13	Merthiolate solution and ointment.....	4	3.0	2.9	0.1	3.9	4.3	-0.4
10/13 to 10/17	Petrolatum gauze.....	4	2.9	9.8	-6.9	4.3	3.7	0.6
10/17 to 10/20	Merthiolate ointment.....	3	9.8	7.9	1.9	3.7	3.4	0.3
10/20 to 10/24	Merthiolate ointment.....	4	7.9	5.4	2.5	3.4	2.8	0.6
10/17 to 10/24	Merthiolate ointment (summary).....	7	9.8	5.4	4.4	3.7	2.8	0.9
10/24 to 10/31	Mercurochrome and petrolatum.....	7	5.4	6.2	-0.8	2.8	2.6	0.2
11/ 1 to 11/ 8	Ultraviolet irradiation and petrolatum gauze dressing..	7	6.2	6.6	-0.4	2.6	2.8	-0.2
11/ 8 to 11/12	Merthiolate ointment.....	4	6.6	7.4	-0.8	2.8	...	...
11/13 to 11/19	Ultraviolet irradiation and merthiolate ointment.....	6	7.4	7.1	0.3	...	3.0	...
11/19 to 11/23	Ultraviolet irradiation and petrolatum gauze.....	4	7.1	5.3	1.8	3.0	3.3	-0.3
11/23 to 11/28	Ultraviolet irradiation and dry dressing.....	5	5.3	5.7	-0.4	3.3	3.9	-0.6
11/28 to 12/ 6	Merthiolate ointment.....	8	5.7	2.7	3.0	3.9	2.6	1.3
12/ 6 to 12/13	Petrolatum gauze.....	7	2.7	3.6	-0.9	2.6	3.8	-1.2
12/13 to 12/26	Irradiated petrolatum ointment.....	13	3.6	4.7	-1.1	3.8	3.9	-0.1
12/26 to 1/ 3	Merthiolate ointment.....	8	4.7	4.9	-0.2	3.9	4.4	-0.5
1/ 3 to 1/10	Mercurochrome and petrolatum gauze.....	7	4.9	1.95	+2.95	4.4	4.4	0
1/10 to 1/18	Merthiolate ointment.....	8	1.95	2.4	-0.45	4.4	3.8	0.6
1/18 to 1/25	Merthiolate ointment .....	7	2.4	1.8	0.6	3.8	3.6	0.2
1/10 to 1/25	Merthiolate ointment (summary).....	15	1.95	1.8	0.15	4.4	3.6	0.8
1/25 to 2/ 1	Mercurochrome and petrolatum gauze.....	6	1.8	3.55	-1.75	3.6	3.8	-0.2
2/ 1 to 2/ 9	Merthiolate ointment.....	8	3.55	2.7	0.85	3.8	4.0	-0.2
2/ 9 to 2/15	Peruvian balsam.....	6	2.7	3.3	-0.6	4.0	3.2	0.8

\* Laminectomy on 10/5.

wounds at frequent intervals, notwithstanding the differences in the mode of dressing, forces the conclusion that the rhythm of healing was set mainly by factors acting at a distance rather than locally. As the parallelism among the curves is not constant, there were times when local forces must have predominated, but there is little evidence that the type of dressing materially affected these forces. These observations apply to the curves of healing based on measurement of both the volume of the wound, as shown in chart 5, and the area of the wound.

CASE 5.—J. F., a boy of 14 with a tumor of the spinal cord extending from the upper thoracic segments to the cauda equina, acquired three large decubitus ulcers, located over each hip and the sacrum. Throughout the period of investi-

TABLE 5.—*Effect of Dressings on a Decubitus Ulcer in the Left Trochanteric Area*

Date	Mode of Dressing	Period of Appli- cation, Days	Volume of Ulcer, Cc.			Area of Ulcer, Sq. in.		
			Start	End	Change	Start	End	Change
8/13 to 8/15	Dry dressing.....	2	10.0	10.3	—0.3	1.5	1.5	0.0
8/15 to 8/17	Wet merthiolate.....	2	10.3	12.0	—1.7	1.5	1.4	0.1
9/ 8 to 9/10	Dry dressing.....	2	2.5	3.1	—0.6	1.2	1.5	—0.3
9/10 to 9/13	Dry dressing.....	3	3.1	2.8	0.3	1.5	1.4	0.1
9/13 to 9/17	Dry dressing.....	4	2.8	4.8	—2.0	1.4	1.3	0.1
9/ 8 to 9/17	Dry dressing (summary).....	9	2.5	4.8	—2.3	1.2	1.3	—0.1
9/17 to 9/19	Wet merthiolate.....	2	4.8	2.1	2.7	1.3	1.2	0.1
9/19 to 9/21	Dry dressing.....	2	2.1	3.3	—1.2	1.2	1.4	—0.2
9/21 to 9/24	Thio cresol 2 days, solution of sodium chloride 1 day.....	3	3.3	4.6	—1.3	1.4	1.3	0.1
9/24 to 9/26	Thio cresol.....	2	4.6	3.3	1.3	1.3	1.1	0.2
9/21 to 9/26	Thio cresol.....	5	3.3	3.3	0.0	1.4	1.1	0.3
9/26 to 10/1	Solution of sodium chloride... Thio cresol.....	5 2	3.3 2.3	2.3 1.7	1.0 0.6	1.1 1.0	1.0 1.0	0.1 0.0
10/ 1 to 10/3	Solution of sodium chloride... Thio cresol.....	2 3	2.3 1.7	1.7 3.7	0.6 —2.0	1.0 1.0	1.0 1.2	0.0 —0.2*
10/ 3 to 10/6	Solution of sodium chloride... Solution of sodium chloride... Solution of sodium chloride (summary).....	3 3 6	3.7 3.7 1.7	2.6 2.6 2.6	1.1 —0.9	1.2 1.0	1.5 1.5	—0.3 —0.5
10/ 9 to 10/13	Merthiolate ointment.....	4	2.6	5.5	—2.9	1.5	1.2	0.3
10/13 to 10/17	Petrolatum gauze.....	4	5.5	5.6	—0.1	1.2	1.4	—0.2
10/17 to 10/20	Merthiolate ointment.....	3	5.6	3.6	2.0	1.4	1.8	—0.4
10/20 to 10/24	Merthiolate ointment.....	4	3.6	2.4	1.2	1.3	1.5	0.3
10/17 to 10/24	Merthiolate ointment (sum- mary).....	7	5.6	2.4	3.2	1.4	1.5	—0.1
10/24 to 10/31	Mercurchrome and petrola- tum gauze.....	7	2.4	3.1	—0.7	1.5	1.4	0.1
11/ 1 to 11/ 8	Ultraviolet irradiation and petrolatum gauze.....	7	3.1	5.3	—2.2	1.4	1.7	—0.3
11/ 8 to 11/12	Merthiolate ointment.....	4	5.3	3.8	1.5	1.7	...	...
11/12 to 11/19	Ultraviolet irradiation and merthiolate ointment.....	7	3.8	2.8	1.0	...	1.9	...
11/19 to 11/23	Ultraviolet irradiation and petrolatum gauze.....	4	2.8	2.4	0.4	1.9	1.6	0.3
11/23 to 11/28	Ultraviolet irradiation and dry dressing.....	5	2.4	3.4	—1.0	1.6	1.6	0.0
11/28 to 12/ 6	Merthiolate ointment.....	8	3.4	0.8	2.6	1.6	1.5	0.1
12/ 6 to 12/13	Petrolatum gauze.....	7	0.8	1.4	—0.6	1.5	2.4	—0.9
12/13 to 12/26	Irradiated petrolatum oint- ment.....	13	1.4	2.1	—0.7	2.4	1.9	0.5
12/26 to 1/ 3	Merthiolate ointment.....	8	2.1	1.3	0.8	1.9	2.1	—0.2
1/ 3 to 1/10	Mercurchrome and petrola- tum gauze.....	7	1.3	1.2	0.1	2.1	1.7	0.4
1/10 to 1/18	Merthiolate ointment.....	8	1.2	1.0	0.2	1.7	2.0	—0.3
1/18 to 1/25	Merthiolate ointment.....	7	1.0	1.3	—0.3	2.0	2.1	—0.1
1/10 to 1/25	Merthiolate ointment (sum- mary).....	15	1.2	1.3	—0.1	1.7	2.1	—0.4
1/25 to 2/ 1	Mercurchrome and petrola- tum gauze.....	7	1.3	1.3	0.0	1.7	2.1	—0.1
2/ 1 to 2/ 9	Merthiolate ointment.....	8	1.3	1.3	0.0	2.2	2.5	—0.3
2/ 9 to 2/15	Peruvian balsam.....	6	1.3	3.1	—1.5	2.5	2.9	—0.4

\* Laminectomy on 10/5.

gation, of approximately six months, there was an irregular fever, the temperature ranging from 97 to 101 F., probably due to pyelonephritis, but the patient remained in a good nutritional state. Laminectomy was performed twice, revealing almost total destruction of the cord, and no functional recovery followed incomplete removal of the tumor. Studies on the rate of healing of the three ulcers were not instituted until all were clean and granulating. The observations are summarized in tables 4, 5 and 6.

Similar reparative phenomena occurred in the three wounds. After initial rapid cicatrization the velocity of healing became exceedingly slow. Ultimately the sacral ulcer became entirely epithelialized, but when the two trochanteric ulcers had decreased to a certain size, the process of repair could not be brought to completion. Extreme care was employed to minimize the effects of pressure: the patient rested constantly on either an air ring or an air mattress; the ulcers were further protected with soft cotton pads, and the position was changed every two hours, day and night. Notwithstanding these measures and persistent treatment with local agents—antiseptic, stimulant and inert—it was impossible to effect total healing during five months of effort, after which the patient was transferred from the hospital. The ulcers showed fluctuation in size from time to time, but the tables indicate that to none of the substances tested can a consistent therapeutic effect be attributed. Several surgical consultants commented on the favorable appearance of the ulcers; almost invariably the granulations were clean and red, and

TABLE 6.—*Effect of Dressings on a Decubitus Ulcer over the Left Sacrum*

Date	Mode of Dressing	Period of Appli- cation, Days	Volume of Ulcer, Cc.			Area of Ulcer, Sq. In.		
			Start	End	Change	Start	End	Change
8/ 8 to 8/10	Dry dressing.....	2	10.3	9.8	0.5	3.3	3.5	-0.2
8/10 to 8/11	Dry dressing.....	1	9.8	9.7	0.1	3.5	3.3	0.2
8/ 8 to 8/11	Summary of dry dressing.....	3	10.3	9.7	0.4	3.3	3.3	0.0
8/11 to 8/13	Wet merthiolate.....	2	9.7	11.8	-2.1	3.3	3.2	0.1
8/13 to 8/15	Dry dressing.....	2	11.8	8.9	2.9	3.2	3.1	0.1
8/15 to 8/17	Wet merthiolate.....	2	8.9	10.0	-1.1	3.1	3.6	-0.5*
9/ 8 to 9/10	Dry dressing.....	2	...	...	...	1.3	1.3	0.0
9/10 to 9/13	Dry dressing.....	3	...	...	...	1.3	1.2	0.1
9/13 to 9/17	Dry dressing.....	4	...	...	...	1.2	1.3	-0.1
9/ 8 to 9/17	Summary of dry dressing.....	9	...	...	...	1.3	1.3	0.0
9/17 to 9/19	Wet merthiolate.....	2	...	...	...	1.3	1.3	0.0
9/19 to 9/21	Dry dressing.....	2	...	...	...	1.3	1.0	0.3
9/21 to 9/24	Thioeresol 48 hours; solution of sodium chloride 24 hours.	3	...	...	...	1.0	0.9	0.1
9/24 to 9/26	" " " "	2	...	...	...	0.9	1.1	-0.2
9/21 to 9/26	" " " "	5	...	...	...	1.0	1.1	-0.1
9/26 to 10/ 1	" " " "	5	...	...	...	1.1	1.3	-0.2
10/ 1 to 10/ 3	Thioeresol.....	2	...	...	...	1.3	1.1	0.2
10/ 3 to 10/ 6	Solution of sodium chloride...	3	...	...	...	1.1	0.8	0.3†
10/ 6 to 10/ 9	Petrolatum gauze.....	3	...	...	...	0.8	0.9	-0.1
10/ 9 to 10/13	Merthiolate ointment.....	4	...	...	...	0.9	0.5	0.4
10/13 to 10/17	Petrolatum gauze.....	4	...	...	...	0.5	0.05	0.45

\* Laminectomy.

† Laminectomy on 10/5.

a fresh epithelial margin was present. It must be concluded that under the existing trophic conditions, the agents employed locally had insufficient effect on the processes of repair to bring about healing.

#### SUMMARY OF OBSERVATIONS ON WOUNDS

Tables 7 and 8 present a summary of the data obtained with all the agents investigated on the entire series of patients. In the instances in which the wound studied failed to heal (not including those in which observations were discontinued during the progress of satisfactory repair) the plotting of curves of healing was obviously impossible, which necessitated a different method of evaluation. Instead of classifying repair as accelerated, retarded or average for a given period of observation, I have assessed the agent applied locally on the basis of whether

the size of the wound increased, decreased or underwent no change. With both types of wounds, however, healing and nonhealing, the results were essentially identical. The observation made on the individual

TABLE 7.—*Effect of Dressings on Wounds Which Underwent Healing*

Dressing	Number of Patients Treated	Observed Effect on Wounds				Percentage Effect on Rate of Healing		
		Number of Observations	Rate of Healing			Accelerated	Retarded	Average
			Accelerated	Retarded	Average			
Merthiolate ointment 1:2,000.....	9	68	27	23	18	39.7	33.8	26.5
Merthiolate solution 1:1,000.....	5	26	10	8	8	38.4	30.8	30.8
Petrolatum gauze.....	6	36	13	11	12	36.1	30.6	33.3
Dry dressing.....	7	19	4	9	6	21.1	47.4	31.5
Physiologic solution of sodium chloride.....	2	11	4	3	4	36.4	27.3	36.4
Mercurchrome and petrolatum gauze.....	3	8	..	3	5	....	37.5	62.5
Thioresol ointment (0.25%).....	3	10	1	5	4	10.0	50.0	40.0
Zinc peroxide paste.....	4	6	..	4	2	....	66.7	33.3
Irradiated petrolatum ointment	1	2	..	1	1	....	50.0	50.0
Peruvian balsam.....	1	2	1	1	..	50.0	50.0	....
Zinc oxide paste boot.....	1	1	..	..	1	....	....	100.0
Allantoin solution (0.6%).....	2	4	2	1	1	50.0	25.0	25.0
		193	62	69	62	32.1	35.7	32.1

TABLE 8.—*Effect of Dressings on Wounds Which Failed to Heal*

Dressing	Number of Pa- tients Treated	Observed Effect on Wounds			Percentage Effect on Wound Size			
		Number of Observation Periods	Size of Wound			Decreased	Increased	Unchanged
			Decreased	Increased	Unchanged			
Merthiolate ointment 1:2,000.....	3	51	31	19	1	60.8	37.3	1.9
Merthiolate solution 1:1,000.....	1	15	6	8	1	40.0	53.3	6.7
Petrolatum gauze.....	3	15	4	11	..	26.7	73.3	...
Dry dressing.....	2	27	16	9	2	59.3	33.3	7.4
Physiologic solution of sodium chloride.....	1	12	7	5	..	58.3	41.7	...
Mercurchrome and petrolatum gauze...	2	15	6	7	2	40.0	46.7	13.3
Thioresol solution.....	1	15	11	3	1	73.3	20.0	6.7
Zinc peroxide ointment.....	1	1	1	..	..	100.0	...	...
Irradiated petrolatum ointment.....	2	7	2	5	..	28.6	71.4	...
Peruvian balsam.....	1	4	1	3	..	25.0	75.0	...
Zinc oxide paste boot.....	1	1	1	..	..	100.0	...	...
Ultraviolet irradiation.....	1	4	..	3	1	...	75.0	25.0
Ultraviolet irradiation and petrolatum gauze.....	1	8	3	5	..	37.5	62.5	...
Ultraviolet irradiation and merthiolate ointment.....	1	2	2	..	..	100.0	...	...
		177	91	78	8	51.4	44.1	4.5

patient that the local dressing did not consistently affect the course of cicatrization is substantiated by the sum total of results with each agent at all extensively tested.

In wounds which healed comparison may be made between the effect of merthiolate ointment and that of petrolatum gauze, which was used as a control, and between the effect of a solution of merthiolate and

that of physiologic solution of sodium chloride, which was used as a control. In thirty-six observations on six patients, repair under a dressing of petrolatum gauze was accelerated in 36.1 per cent, retarded in 30.6 per cent and of average rate in 33.3 per cent. The effect of merthiolate ointment appears slightly superior, healing being accelerated in 39.7 per cent, retarded in 33.8 per cent and average in 26.5 per cent of sixty-eight applications on nine patients. Similarly, when the effect of a physiologic solution of sodium chloride was contrasted with that of a solution of merthiolate a slight superiority was noted in favor of the latter. Yet a decided effect on healing can hardly be attributed to any of these four agents, since there was approximate correspondence in the percentage incidence of an accelerated, average or retarded rate of repair.

With dry gauze dressing, mercurochrome and thiocresol ointment healing was preponderantly either retarded or of average velocity; hence these substances appear to exert a somewhat detrimental action. In a number of wounds which had been cicatrizing steadily during several successive periods of observation, it was noted that the application of mercurochrome coincided with definite retardation in the rate of healing. Thiocresol contains the sulfhydryl group, which Hammett and Reimann considered the specific hormone for cellular proliferation. Not only these authors but Brunsting and Simonsen,<sup>20</sup> Birnbaum<sup>21</sup> and Sutton<sup>22</sup> have reported favorably on the value of sulfhydryl preparations. In my experience, however, I have found during ten periods of observation on three patients treated with thiocresol dressings that healing was accelerated only once, retarded five times and average four times.

The study of wounds which progressed to healing comprised treatment with twelve different local dressings during a total of one hundred and ninety-three periods of observation. The agents used either were admittedly inert or were presumed to further the reparative functions through a stimulant or antiseptic action. No single substance proved of outstanding worth or particularly detrimental to repair. The effect of the entire group was to accelerate the velocity of healing in 32.1 per cent, to retard it in 35.7 per cent and not to alter it in 32.1 per cent of the instances in which these vulneraries were employed. Therefore, it must be concluded that whatever slight effect these substances may exert, they do not significantly influence the course of healing.

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20. Brunsting, L. A., and Simonsen, D. G.: Cutaneous Ulcers Treated by Sulphydryl Containing Amino-Acid Cysteine, *J. A. M. A.* **101**:1937 (Dec. 16) 1933.

21. Birnbaum, I. R.: *Ann. Surg.* **96**:467, 1932.

22. Sutton, L. E.: Thioglycerol: A More Stable Sulphydryl Compound for Use in the Healing of Wounds, *J. A. M. A.* **104**:2168 (June 15) 1931.

On consideration of the results obtained in the investigation of nonhealing wounds, a similar conclusion is reached. Not every agent, however, had an identical effect on the two types of wounds—healing and nonhealing. While with the former class of wounds, both merthiolate ointment and merthiolate solution were somewhat superior to their respective controls, petrolatum gauze and physiologic solution of sodium chloride, with the latter type their actions appear divergent, the ointment having a favorable influence on healing and the solution an unfavorable influence as compared with the controls. Furthermore, in contrast to the findings regarding wounds which healed, dry gauze dressing seems superior to petrolatum gauze, and thiocresol apparently is a definite stimulant.

It will be observed, however, on more detailed scrutiny of these results that the two substances most thoroughly tested were merthiolate ointment and dry gauze dressing. The effects of these agents on the rate of healing are substantially alike; neither produced a marked acceleration in the velocity of repair. Throughout this study I have noted that as the number of periods of observation in the evaluation of any given material increased, there occurred a counterbalancing of favorable and unfavorable results until the two approximated. Examination of the agents listed in the tables and their respective number of periods of observation reveals this tendency. The necessity for accumulating a great body of observations before drawing conclusions as to the value of any preparation and the likelihood of fallacious conclusions after only a limited number of observations are thus strongly indicated. These considerations probably account for the difference in results obtained in the evaluation of the effects of certain agents on both healing and nonhealing wounds.

During the entire investigation on wounds which could not be caused to cicatrize totally, fourteen agents—antiseptic, stimulant and inert—were applied in one hundred and seventy-seven periods of observation; their effect was a decrease in the size of the wound in 51.4 per cent of the cases, an increase in 44.1 per cent and no change in 4.5 per cent. The values obtained with the antiseptic merthiolate ointment and the inert dry gauze dressing somewhat surpass the general average but reveal no markedly efficacious action on repair. Consequently, the statement seems warranted that in nonhealing wounds, just as in healing wounds, the agents tested by local application have not significantly affected the reparative functions.

Furthermore, I have found in the course of my work that no antiseptic ever sterilized or even significantly altered the cultural characteristics of any of the wounds studied, which were of the type surgically



clean but bacteriologically contaminated. Hill<sup>23</sup> reported the failure of a single application of a 2 per cent solution of mercurochrome to sterilize an infected wound. Both Carrel<sup>24</sup> and Wright<sup>25</sup> have expressed the conviction that antiseptics do not sterilize heavily infected wounds. Since infection admittedly inhibits repair, this failure of antiseptics to affect the cultural status of wounds affords confirmation on bacteriologic grounds for the point of view that I have reached on the basis of measurement, that these agents do not greatly influence the rate of healing.

My observations on the effect of local dressings on wound healing may be summarized as follows:

1. During the cicatrization of a given wound agents repeatedly applied locally during alternate periods have failed to influence the rate of repair in a consistent manner.

2. Among the substances studied in this investigation no single agent, irrespective of its nature, proved outstandingly favorable or unfavorable in its action.

3. A wound will heal or fail to heal regardless of the material applied locally. The effects exerted on the processes of repair by agents applied locally are of relatively minor significance and are outweighed by other forces, many of which are probably nonlocal.

#### EFFECT OF MERTHIOLATE ON TISSUES IN VITRO

In carrying out this investigation on local therapeutic agents I devoted particular attention to the recently introduced antiseptic merthiolate. Chemically this substance is the sodium salt of ethylmercurithiosalicylic acid. Tests of its antiseptic potency and toxicity have established that dilutions nontoxic to animals are bactericidally effective against cultures in vitro in the presence of serum. I have already presented the results of its clinical trial, in which a slight superiority over control agents, petrolatum gauze or physiologic solution of sodium chloride, was possibly manifested, but without demonstration that it caused any marked alteration in the course of healing.

In order to check this clinical evaluation, the degree of selectivity of the action of merthiolate on bacteria and on living cells was ascertained by studies in vitro.<sup>26</sup> The concept that the comparative toxicity to bacteria and to cells of the body provided the proper criterion for

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23. Hill, J. H.: The Action of Mercurochrome and Other Drugs on Normal Human Skin and in Infected Wounds, *J. A. M. A.* **105**:100 (July 13) 1935.

24. Carrel, A., and Dehelly, G.: Treatment of Infected Wounds, New York, Paul B. Hoeber, Inc., 1916.

25. Wright, A.: *Brit. M. J.* **2**:629, 1915.

26. The experiments on tissue cultures were performed in the laboratory of Dr. J. M. Hogue.

the assessment of an antiseptic was first practically applied by Lambert<sup>27</sup> in 1916 through the use of tissue cultures. Since that date cultures *in vitro* have been employed in determining the efficiency of antiseptics by Lambert and Meyer,<sup>28</sup> German,<sup>29</sup> Buchsbaum and Bloom<sup>30</sup> and Salle and Lazarus,<sup>31</sup> although no standard technic was followed. All these investigators, however, agreed in the finding that every antiseptic tested had a more deleterious effect on tissues than on bacteria.<sup>32</sup> Buchsbaum and Bloom<sup>30</sup> studied merthiolate and expressed their results in terms of an index of relative toxicity equal to the ratio of the greatest dilution that killed the bacterium used to the greatest concentration in which cells showed approximately normal growth. It was found that the index for merthiolate was 0.9, the highest obtained in a group including phenol, iodine, mercurochrome and metaphen, thereby establishing merthiolate as the least toxic of the agents evaluated, but not a theoretically ideal antiseptic (the ratio for which should exceed 1).

Since my work in this field will be reported in detail subsequently, I shall merely cite in brief the data pertaining to merthiolate. Using explants of skin from a chick embryo cultivated in a liquid medium, I determined: (1) the least concentration which killed *Staph. aureus* in the culture medium alone, (2) the least concentration which killed this organism in the presence of the explant and (3) the least concentration which was deleterious to the growth of the explant.

Under the experimental conditions established, dilutions of merthiolate up to 1:100,000 were invariably bactericidal in the culture medium alone. Yet in the presence of the explant a concentration of 1:20,000 was required to destroy the organism; with a concentration of 1:100,000 growth always occurred, and for intermediate ranges results depended on the size of the explant used in making the culture. Concerning the effect of merthiolate on the tissue alone, it was observed that dilutions up to 1:600,000 invariably killed the explant while dilutions of 1:1,200,000 still prevented normal growth, as indicated by control cultures.

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27. Lambert, R. A.: *J. Exper. Med.* **24**:683, 1916.

28. Lambert, R. A., and Meyer, J. R.: *Proc. Soc. Exper. Biol. & Med.* **23**:429, 1926.

29. German, W. J.: *Effect of Some Antiseptics on Tissues in Vitro*, *Arch. Surg.* **18**:1920 (April, pt. 2) 1929.

30. Buchsbaum, R., and Bloom, W.: *Proc. Soc. Exper. Biol. & Med.* **28**:1060, 1931.

31. Salle, A. J., and Lazarus, A. S.: *Proc. Soc. Exper. Biol. & Med.* **32**:665, 937, 1057, 1119 and 1481, 1935.

32. Salle and Lazarus have recently reported iodine in the form of compound solution of iodine to be more toxic *in vitro* to bacteria than to tissues.

These observations establish that there is a more toxic action by merthiolate on connective tissue and epithelial cells than on bacteria, but most striking is the marked depression in antiseptic potency produced by the concomitant presence of tissue and micro-organisms. In view of the great difference in conditions prevailing in wounds on the body and in cultures in vitro, it is my belief that these observations are not directly applicable to the problem of the influence of antiseptics on wound repair. None the less, this evidence must be regarded as indicating that such influence in all probability will not be favorable, a point of view consistent with the conclusions previously derived from the actual study of wound healing.

#### CONCLUSION

Through a method of quantitative evaluation of the effect of local agents on the velocity of wound repair it has been demonstrated that the substances tested, including antiseptics, stimulants and inert materials, failed to affect significantly the processes of repair. Factors other than the local dressing appear to play the dominant rôle in determining the rate of wound healing.

# ESTRUS CYCLES IN MICE OF CANCEROUS AND NONCANCEROUS STRAINS

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It has been shown by Lacassagne<sup>1</sup> and more recently by Burrows<sup>2</sup> that carcinoma of the breast may be produced in male mice by the administration of large doses of estrogenic hormone. These observations are of great importance because this is the first instance of direct association of malignant neoplasia with an excess of a hormone normally produced by the organism. The question immediately arising is: Does spontaneous carcinoma of the breast in mice result from hypersecretion of estrogenic hormone over a long period?

As a result of the classic works of Allen,<sup>3</sup> and of Allen and Doisy and their associates,<sup>4</sup> the secretion of estrogenic hormone may be studied readily in the intact mouse by observation of the estrus cycle. Proestrus and estrus correspond to the period of ripening and the period of maximum activity of the graafian follicle. Metestrus and diestrus are periods in which no appreciable amount of estrogenic hormone is liberated.

Few reports are found in the literature of studies in which comparisons were made of estrus cycles in mice belonging to strains with high and low incidence of carcinoma of the breast. Lacassagne<sup>5</sup> mentioned briefly that in two strains—one in which carcinoma developed between the fourth and the sixth month of life and one in which it appeared between the tenth and the twelfth month—the average duration of estrus cycles varied considerably. In the former the cycle was regular and of the five day type; in the latter it was irregular and the periods of

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1. Lacassagne, A.: Apparition de cancers de la mamelle chez la souris mâle soumise à des injections de folliculine, *Compt. rend. Acad. d. sc.* **195**:630, 1932.

2. Burrows, Harold: Pathological Changes Induced in the Mamma by Estrogenic Compounds (Hunterian Lecture), *Brit. J. Surg.* **23**:191 (July) 1935.

3. Allen, E.: The Oestrous Cycle in the Mouse, *Am. J. Anat.* **30**:297, 1922.

4. Allen, E.; Doisy, E. A., and others: The Hormone of the Ovarian Follicle, *Am. J. Anat.* **34**:133, 1924.

5. Lacassagne, A., and Nyka, W.: A propos d'une pathogénie de l'adénocarcinome mammaire: recherches de la folliculine dans le colostrum, *Compt. rend. soc. de biol.* **116**:844, 1934.

heat were relatively brief. Harde<sup>6</sup> mentioned briefly that in strains in which the incidence of carcinoma was high the cycles were a little more prolonged than in the strains in which it was low. To be of real significance, however, marked consistent differences should be noted in the estrus cycles of different strains, for, as has been repeatedly shown, there is naturally a species variation and even an individual variation in length and type of the estrus cycle in mice.

The following observations were undertaken to compare the estrus cycles (follicular secretion) in three groups of mice, one composed of animals from a strain in which spontaneous carcinoma of the breast has never been observed, the second including mice belonging to a strain in which the incidence was high but which did not at the time of the experiment exhibit tumors of the breast and the third including animals of the same strain as those in group two which exhibited carcinoma of the breast during the period of observation.

#### EXPERIMENTATION

*Material and Methods.*—The mice used for study of the effects of various doses of theelin were albinos of unrecorded ancestry, obtained from a dealer.

The mice of the strain in which the incidence of cancer was high were obtained through the kindness of Dr. C. C. Little from the Roscoe B. Hyde Memorial Laboratory, in Bar Harbor, Maine. They were of the dilute brown strain, in which the incidence of cancer is stated to be 58.68 per cent. This strain (Little dba) has been fully described.<sup>7</sup> The mice of noncancerous strain, also obtained from Dr. Little, were black mice of the strain C 57. No tumors have been observed in this stock since inbreeding began, in 1921.<sup>8</sup>

Vaginal smears were made daily at about the same hour by means of a ball-tipped glass rod. The smears were stained with hematoxylin and eosin. In recording the results graphs were made designating O, estrus, the stage of cornification; M, metestrus, the stage of invasion by leukocytes; D, diestrus, the resting stage, and P, proestrus, the period in which the epithelial cells are nucleated and cornified (charts 1, 2 and 3). Secretion of estrogenic substance is denoted by the P and O stages only.

*Experiment 1.*—Although it has been demonstrated previously that the length of the period of heat is roughly proportional to the amount of estrogenic substance secreted, a preliminary experiment was performed to confirm this observation.

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6. Harde, E.: Influence des hormones et des vitamines dans la production des adéno-carcinomes mammaires chez la souris, *Compt. rend. Soc de biol.* **116**: 999, 1934.

7. Murray, W. S.: The Breeding Behavior of the Dilute Brown Stock of Mice (Little Db), *Am. J. Cancer.* **20**:573, 1934.

8. Murray, W. S., and Little, C. C.: The Genetics of Mammary Tumor Incidence in Mice, *J. Genetics* **20**:466, 1935.

Six ovariectomized female albino mice 8 months of age were given injections as follows: One received 100 mouse units of theelol<sup>9</sup> in oil, one received 500 mouse units and one received 1,500 mouse units. Of the remaining three, each received 12 mouse units of theelin in aqueous solution. In the first three estrus was established in seventy-two hours and lasted for five, four and five days, respectively. Of the latter three, two failed to respond and seventy-two hours after injection one exhibited full estrus, which lasted twenty-four hours.

Thus, a prolonged period of heat represents a relatively large amount of estrogenic hormone liberated, whereas a short period is indicative of a small amount. However, among several animals each exhibiting prolonged periods it appears that there may be a wide variation in the amount of hormone liberated.

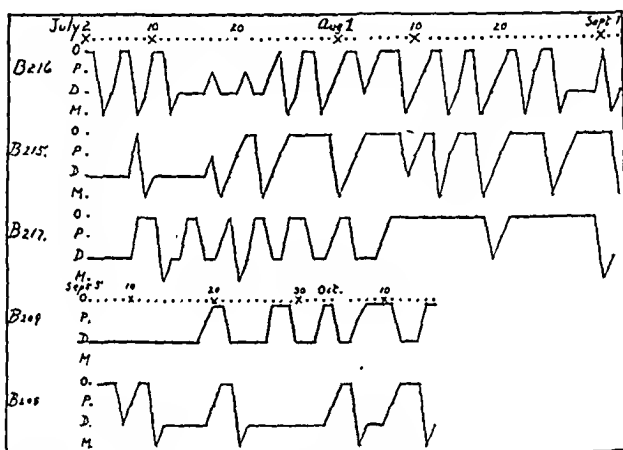


Chart 1.—Black mice of a noncancerous strain. The total number of days was two hundred and seventy-one, of which one hundred and thirty-nine (51.2 per cent) were spent in heat.

TABLE 1.—*Estrus Cycles in Three Groups of Mice*

Animals*	Total Number of Days Observed	Number of Estrus Cycles	Average Length of Cycle, Days	Percentage of Time in Heat
Group 1, five black mice, noncancerous strain.....	271	41	6.6	51.2
Group 2, three dilute brown cancerous strain, noneancer bearing .....	159	37	4.9	40.7
Group 3, five dilute brown cancerous strain bearing car- cinoma of the breast.....	215	34	5.9	32.5

\* All mice were approximately 1 year old.

*Experiment 2.*—The comparison of the estrus cycles in the three groups of mice described are summarized in the table.

*Experiment 3.*—In the final experiment three mice bearing carcinoma of the breast were ovariectomized and vaginal smears were made daily

9. The theelol was supplied by Parke, Davis & Co.

for one month, beginning one week after operation. No estrus periods were noted during this time; the smears all exhibited characteristics of the diestrus, or resting state.

## COMMENT

An analysis of the data given in the table shows that in the small group of animals studied (of carefully controlled heredity) the average

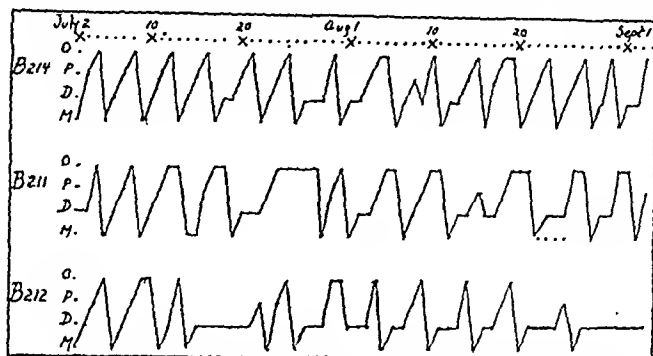


Chart 2.—Brown mice of a cancerous strain, but without cancer at the time of observation. The total number of days was one hundred and eighty-nine, of which seventy-seven (40.74 per cent) were spent in heat.

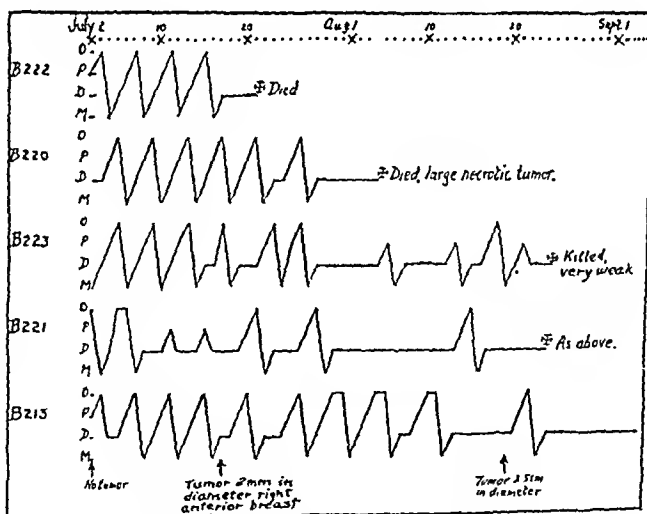


Chart 3.—Brown mice of a cancerous strain, bearing cancer at the time of observation. The total number of days was two hundred and fifteen, of which seventy (32.56 per cent) were spent in heat.

estrus cycle in the noncancerous strain was longer than that in the cancerous strain. The percentage of time in heat (flooding of the organism by estrogenic hormone) was also somewhat greater in the noncancerous strain. The latter observation may be partially explained by the fact that toward the end of the periods of observation in the cancer-bearing

animals the increasing size of the tumor affected the general health, and it is well known that estrus tends to be inhibited in animals that are not in good condition.

Thus, in these observations, no evidence was obtained of chronic hypersecretion of estrogenic hormone as a cause of spontaneous carcinoma of the breast in mice.

These results are in accord with those recently reported by Bonser,<sup>10</sup> who also compared the estrus cycles in mice belonging to strains of high and low incidence of carcinoma. This author did not differentiate between those mice of the former strain actually bearing tumors and those not bearing tumors. It was found that the average length of the cycles differed only by one tenth of a day and that the periods of heat averaged two tenths of a day longer in the strain in which the incidence was low. This author further showed that in ovariectomized mice of these strains, injections of estrogenic substances provoked a slightly greater response in animals belonging to the strain in which the incidence of carcinoma was low.

Loeb<sup>11</sup> and Cori<sup>12</sup> showed that the incidence of cancer of the breast in female mice belonging to a strain in which the incidence of carcinoma was high was greatly reduced if ovariectomy was performed at a very early age and that the incidence was not affected if this operation was performed after the eighth month of life. Since spontaneous carcinoma rarely if ever develops in immature breasts, it would appear that the rôle of the ovaries in the development of carcinoma of the breast is secondary, in that ovarian secretion is necessary for the development of the mammary gland to an adult stage, after which malignant neoplasia may occur.

Thus, the demonstration by Lacassagne and Burrows that estrogenic substance in large doses may cause carcinoma of the breast in male mice might well be interpreted as a demonstration of malignant degeneration resulting from the subjection of a tissue over long periods to a strong extraneous specific growth stimulus (estrogenic substance acting on the mammary ducts). It is not apparently a demonstration of the natural mechanism for spontaneous malignant degeneration in the mammary glands of mice.

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10. Bonser, Georgiana: A Comparison of the Normal Oestrous Cycle and of the Response to the Administration of Oestrin in Two Strains of Mice Differing Greatly in Incidence of Spontaneous Mammary Cancer. *J. Path. & Bact.* **16**:33, 1935.

11. Loeb, L.: Internal Secretion as a Factor in the Origin of Tumors, *J. M. Research* **40**:477, 1919.

12. Cori, C. F.: The Influence of Ovariectomy on the Spontaneous Occurrence of Mammary Carcinomas of Mice, *J. Exper. Med.* **45**:983, 1927.



## SUMMARY

Because injections of large doses of estrogenic hormone have been shown to cause mammary carcinoma in male mice (Lacassagne, Burrows), comparisons are reported between the estrus cycles in female mice belonging to a strain of high incidence of mammary carcinoma and those in females of a noncancerous strain in order to determine whether in the former strain a hypersecretion of the ovary exists to explain the high incidence of cancer of the breast. In the animals studied the periods of heat (period of secretion of estrogenic hormone) were somewhat longer in the animals belonging to the noncancerous strain than in those of the cancerous strain, whether or not they exhibited tumors of the breast. This constitutes evidence against the hypothesis that an excess of secretion of estrogenic hormone by the ovary plays the principal etiologic rôle in spontaneous mammary carcinoma in mice.

## A REVIEW OF UROLOGIC SURGERY

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*(Concluded from page 348)*

### PROSTATE GLAND

*Hypertrophy.*—Teem<sup>36</sup> reviewed 733 consecutive necropsies which were performed in the years 1930 to 1933, inclusive, at the Mayo Clinic, on male patients who were more than 40 years of age. Of these men, 334 (45 per cent) had prostate glands which were larger than normal. The purpose of the investigation was to make a comprehensive study of the gross anatomy of the prostate gland and of the microscopic anatomy of the testis in a large series of cases. It was thought that thorough correlation of the findings in examinations of subjects of all decades of life and, consequently, of prostate glands of all sizes might give some information on the tissue in the testis concerned with the development and maintenance of the prostate gland. Such a study was undertaken, therefore, on the premise that it would be possible to determine from the histologic appearance of a tissue some idea of its function, particularly in the elaboration of an internal secretion. Of the 504 prostate glands studied, 301 were classified as normal, 189 as hypertrophied, and 14 as not as large as normal either in weight or in dimensions.

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36. Teem, M. van B.: The Relation of the Interstitial Cells of the Testis to Prostatic Hypertrophy, *J. Urol.* 34:692 (Dec.) 1935.

The interstitial cells of the testis are numerous at birth, reach their greatest average relative number between the ages of 10 and 19 years, and then gradually and progressively decrease in number as age advances. The decrease in the average relative numbers of interstitial cells in subjects who have hypertrophied and those who have normal prostate glands is about parallel until the age of 69. After that age, the average relative number of interstitial cells among subjects who have hypertrophied prostate glands decreases more rapidly than does that among subjects who have normal prostate glands. A remarkably good state of preservation of the seminiferous tubules and of spermatogenesis was not infrequently encountered between the ages of 40 and 89. Tumor of the interstitial cells of the testis may be associated with a normal or a subnormal size of the prostate gland.

*Hemorrhage.*—Shivers<sup>37</sup> said that severe hemorrhage of prostatic origin, which requires emergency treatment, appears to be rare since only 26 cases have been reported in the literature. In 15 cases it was necessary to enucleate the prostate gland to save the patient's life. In 7 cases reported in the literature and in a case that Shivers observed suprapubic drainage did not control the hemorrhage. The cause of the prostatic ulceration in the latter case was not found but was undoubtedly a significant factor in producing the primary hemorrhage. Emergency prostatectomy is not desirable if any other method can be used to control the bleeding. This is particularly true when renal or cardiovascular disease is present. Instrumentation in this type of prostate would be an important factor in inducing a severe hemorrhage. If the vessel is accessible, cauterization of the bleeding point may stop the hemorrhage. If the bleeding cannot be otherwise controlled, enucleation of the prostate gland is proper.

*Resection.*—Davis<sup>38</sup> reported 748 cases in which transurethral resection of the prostate gland was performed. In his opinion any type of prostate gland may be treated by resection provided the operator has the skill and the perseverance to continue until a satisfactory operation has been consummated. It is generally conceded that resection is suitable in cases of obstruction by bars, contractures or small median and lateral lobes of the gland. When the operator has acquired sufficient skill, the large lateral lobes can also be adequately removed. Two sittings may be necessary for resecting large lateral lobes, although Davis prefers to complete each resection at one operation. From 50 to 75 Gm. of tissue have repeatedly been removed within one and a half hours.

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37. Shivers, C. H. de T.: Uncontrollable Hemorrhage from Benign Prostatic Enlargement: Report of a Case, *J. Urol.* **34**:417 (Nov.) 1935.

38. Davis, T. M.: Transurethral Prostatic Resection with Report of Seven Hundred and Forty-Eight Cases, *South. M. J.* **28**:693 (Aug.) 1935.

An operation of this duration is not any more exhausting to the patient than are two operations of shorter duration. In the two stage operation there is less hemorrhage during the second stage, and, as the lobes have a tendency to collapse toward the midline, removal of tissue is expedited.

If the residual urine measures more than 5 ounces (148 cc.), adequate preliminary preparation is significant. Decompression by means of an indwelling urethral catheter is the method of choice. It has never been necessary or desirable, in Davis' experience, to employ suprapubic cystotomy in the preparatory treatment. When this is done, prostatectomy should be the method of choice, except when there is malignant growth. Vasectomy is not necessary. In this series of 748 cases there were 14 instances of preoperative epididymitis and 21 of postoperative epididymitis. Vasectomy in each of these 748 cases would have subjected too many patients to a needless operation.

When obstruction is caused by a median bar, excision of the bar is sufficient to insure permanent results. If there is enlargement of the median lobe of the prostate gland, the entire median lobe should be removed. If there is hypertrophy of the lateral lobes, at least two thirds of the lateral lobes should be removed. In many cases the lobes are removed to the muscles or the supposed capsule. The anesthesia preferred is caudal and transsacral block anesthesia produced with 1 per cent solution of procaine hydrochloride. It is safe, of sufficient duration and free from undesirable sequelae. In the occasional case in which this anesthesia is not complete, a special needle adapter for the sheath of the resectoscope, which permits the prostate gland to be infiltrated under vision, is used. The improved Davis-Bovie generator produces a cutting current that can be adapted to the particular type of prostate gland that is being resected. The current may be varied from one that sections tissue as well or better than the tube machine with a thin depth of dehydration to one that sections tissue with a zone of dehydration that controls all except the largest arteries. The advantages of these currents are that they permit the resection of fibrous or vascular glands with equal facility and minimal hemorrhage. Sectioning with the McCarthy resectoscope is toward the operator, and when the capacity of the bladder is 8 ounces (236 cc.) or more, repeated sections should be made, and the tissue allowed to fall into the bladder. Hemorrhage rarely interferes with vision until the entire lobe is removed. When the capacity of the bladder is reached, the water is allowed to return through the sheath, and the tip of the sheath is wiggled near the base of the bladder. Many, if not all, of the sections of tissue will come out through the sheath. Bleeding vessels are controlled, and any remaining obstructing tissue in the lobe is removed.

Hemorrhage should be completely controlled in each lobe before removal of tissue from another lobe. If there is median obstruction

of the gland, the tissue is removed to permit an unobstructed view from the verumontanum to the trigon. When one is removing this type of obstruction there always appears to be obstructing tissue at the posterior cut edge. Within the bladder the lateral lobes are removed so that they will be on a level with the walls of the bladder. Within the urethra the lateral lobes are excavated laterally. When the view is from the level of the verumontanum there should be a concavity with the narrow points at the vesical orifice and on a level with the verumontanum. Hemorrhage should be completely controlled before the patient leaves the operating table. All vessels should be coagulated by moving the loop backward and forward over the area. A certain amount of bleeding may have to be tolerated at the apex of the gland, near the external sphincter. This is usually produced by trauma and will subside of itself when the sheath is removed and the catheter is in place. Coagulation in this area is likely to result in damage to the sphincter and must be avoided.

The patient should be kept quiet for forty-eight hours. The retention catheter should be connected to a rubber tube which is connected to a bottle at the bedside. The catheter should then be irrigated by a nurse, when necessary, using cold sterile water with a plunger syringe, suction being employed to remove any clots. Irrigations should be continued until the drainage is clear, a period of usually not more than twenty-four hours.

No difficulty has been experienced with immediate postoperative hemorrhage. It is Davis' opinion that the majority of the reported difficulties have resulted from the use of improper coagulating current or from insufficient care in coagulation; others have resulted from a fall in blood pressure during the operation and a rise several hours afterward. Serious infection has been negligible in this series of 748 cases. The urine contained pus cells for about two months after operation. If the bladder is able to empty completely or if the amount of residual urine is not more than 1 ounce (30 cc.), the infection will clear spontaneously. If sufficient tissue is not removed and obstruction continues, the infection will persist. There were 2 instances of permanent incontinence in the 748 cases: one that was intentional in a case of carcinoma, and the other in a case of benign hypertrophy with injury in the region of the sphincter. In the seven and a half years during which resection of the prostate gland has been used by Davis, 46 patients who had had their prostate glands removed within five years were operated on by resection. Twenty-four of the 748 patients in this series required subsequent resection; 9 of these were operated on within the first six months; 7 who had benign obstruction had a definite recurrence; 8 who had malignant obstruction required one or more resections for continued relief.

Resection of the prostate gland when properly performed has a low mortality. In a series of 416 cases in which resection was done there were no deaths; in another series of 332 resections there were 6 deaths, making a mortality of 0.8 per cent in the total of 748 cases.

Thompson<sup>39</sup> said that until a few years ago urologists agreed that litholapaxy should be employed only when there was no other condition within the bladder requiring operation; hence practically all patients with prostatic enlargement and coincident vesical calculus were subjected to suprapubic operation. As a general rule, this was done in two stages, and the patient therefore spent a long time in the hospital. The development of transurethral prostatic resection has enabled the urologist to remove the offending prostate gland as well as any stones that are present in one operation, thus greatly shortening convalescence. Thompson reports 54 cases in which he has employed this combined procedure. The amount of prostatic tissue which was removed varied from 3 to as much as 47 Gm. The calculi in some cases were as large as 5 cm. in diameter. The incidence of epididymitis, chills and fever and the mortality were no greater in these cases than in similar cases in which prostatic resection only was employed.

Ballenger<sup>40</sup> said that in more than 400 cases in which resection of the prostate gland was done the mortality was about a tenth of what would have been expected if prostatectomy had been performed in the same cases. Many of the patients have been regarded as altogether unfit for prostatectomy if it had been required. He has performed prostatectomy on only 2 patients since he began to use resection of the prostate gland. He seldom performs suprapubic cystotomy; transurethral resection has been found safer than cystotomy, even when the prostate gland is large and has to be removed in two stages. While this may increase the mortality from resection, it will also increase the number of patients who are alive after the employment of relief measures for obstruction of the prostate gland.

Wesson<sup>41</sup> stated that the time to control hemorrhage in resection of the prostate gland is while the patient is anesthetized at the time of operation. He prefers the Herbst bag for this purpose and uses the spark as little as possible, thereby preventing pyelitis. The resection is continued until the bleeding becomes annoying; then the sheath is removed, and the Herbst bag is introduced on a stylet. The end of the catheter is passed through a rubber sponge, the bag is inflated, and the pressure is maintained for about seven minutes. When the sheath

39. Thompson, G. J.: Simultaneous Litholapaxy and Prostatic Resection, Proc. Staff Meet., Mayo Clin. 10:689 (Oct. 30) 1935.

40. Ballenger, E. G., in discussion on Davis,<sup>38</sup> p. 699.

41. Wesson, M. B., in discussion on Davis,<sup>38</sup> p. 699.

is reintroduced, any bleeding will be from large vessels that can be easily seen and fulgurized.

Davis' treatment of the sphincters is anatomically sound. It should be borne in mind, from the urinary standpoint, that the prostate gland is the neck of the bladder, that is, two surgical sphincters that have been invaded by prostate tubules. A sphincter is a muscle whose origin and insertion is in itself. Hence, the external sphincter of the bladder that surrounds the apex of the prostate gland is a true anatomic sphincter of striated muscle fibers. The so-called internal sphincter is a surgical and not a true anatomic sphincter and is composed of smooth muscle fibers. It is not a circular loop but is composed of two arcs of muscles that interlock and close the bladder by a tonsillotome-like action. The fibers of the external longitudinal layer of the bladder, when they reach the vesical orifice, sweep upward and pass over the top, forming a heavy loop or bundle. The inferior arc is composed of fibers from the internal circular layer. They form an oblique loop with one end in the floor of the vesical orifice and the other above the verumontanum. In prostatic resection, laterally and posteriorly, the superficial part of the weaker loop, which is composed of the fibers from the circular layer, is removed along with the hypertrophied gland. The powerful superior arc or bundle, which is situated anteriorly, is protected by not cutting in that sector.

Collings<sup>42</sup> said that certain limitations of transurethral operations must be recognized. Relief has been secured in from 90 to 95 per cent of 75 cases occurring during the last two years in which obstruction of the prostate gland was removed with the knife electrode. Four deaths occurred, in cases in which there was carcinoma of the prostate gland. He has traced 135 patients who were operated on between 1923 and 1933; 16 died within from one month to five years after operation, 6 of heart disease, 3 of pneumonia, 2 of carcinoma of the prostate gland and uremia, 3 of septicemia or pyemia, and 1 of typhoid fever; 1 committed suicide. Of the 119 patients who are living, 77 per cent obtained complete relief, and 23 per cent had some urinary frequency and burning at times. The excision of the prostatic urethra with the knife electrode has given maximal relief with few complications or operative deaths.

Thompson<sup>43</sup> reported that 49 of 1,694 patients subjected to transurethral resection at the Mayo Clinic between Jan. 1, 1913, and Jan. 1, 1935, were again operated on for the relief of urinary obstruction;

42. Collings, C. W.: Endoscopic Excision of Prostatic Obstruction, *J. Urol.* **34**:396 (Nov.) 1935.

43. Thompson, G. J.: Recurrence of Urinary Obstruction Following Transurethral Prostatic Resection, *J. Urol.* **34**:405 (Nov.) 1935.

16 of these 49 patients originally had carcinoma of the prostate gland, 10 a median bar or a contracture of the vesical neck, and 23 an adenomatous enlargement of the type formerly treated by prostatectomy. The 10 patients with a median bar or a contracture of the vesical neck belonged to the group for which the punch operation is recognized to be the operation of choice; symptoms of urinary obstruction recur in a larger proportion of patients of this type than of those with adenomatous enlargement of the prostate. The 23 patients with adenomatous hyperplasia probably all had a certain amount of regrowth of prostatic tissue, although 6 of them reported that they had not been completely relieved by the first operation; in 5 others, definite new growth could be recognized by cystoscopy. In each instance in which there was a recurrence, the stay in the hospital following the second operation was shorter than that after the primary operation; there were no complications. Recurrent obstruction of the urinary tract following transurethral resection will be infrequent in cases in which the primary operation is thorough; if a good functional result is not immediately obtained, it is best to remove more tissue without delay. More deformity of the prostatic urethra results from suprapubic or perineal prostatectomy than from prostatic resection; recurrent intra-urethral proliferation of adenomatous tissue is little, if any, greater after transurethral resection than after prostatectomy. Up to the present, the percentage of cases in which urinary obstruction has recurred after transurethral resection is much less than has been predicted.

#### PENIS

*Carcinoma.*—Barringer<sup>44</sup> abstracted from the records of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, the data in 100 cases of carcinoma of the penis. Sixty-three patients (less than two thirds of the series) apparently and probably had no lesion beyond the primary one of the penis. Fifty-five of these 63 patients have been free from symptoms for periods ranging between one and more than ten years following treatment. Eight patients died of the disease between one and five years after treatment, and 19 (19 per cent) have been well for more than five years.

Thirty-seven patients (more than a third of the series) had metastasis to the groin. In 9 (24 per cent) of these patients, the involvement was controlled for periods of from one to ten years. Radical dissection of the groin was not done by Barringer in any of these 9 patients. The 28 remaining patients died of carcinoma, although 4 lived between two and three years and 1 lived more than three years. Fifteen of

44. Barringer, B. S.: Inguinal Gland Metastases in Carcinoma of the Penis, J. A. M. A. 106:21 (Jan. 4) 1936.



the 28 patients died within the first year. In 22 of the cases there was no microscopic examination of the lesion, while a positive diagnosis of carcinoma was made in 14 cases. In 5 of the 14 cases a positive diagnosis of carcinoma was made by the aspiration method. In 5 of the 9 cases in which the growth was controlled there was a positive pathologic diagnosis of carcinoma of the inguinal lymph nodes. In 3 cases no diagnosis was made, and in 1 case the diagnosis was questionable. Only 2 patients have lived free from symptoms for more than five years. In 4 patients metastasis occurred after treatment was started. In 10 of the 37 patients in whom there was metastasis to the lymph nodes there was infection of the involved lymph nodes. This resulted in the breaking down of the carcinoma into a sloughy ulcerated mass and eventually in the death of the patient. No known treatment can cope with such a situation. Six of the patients came to the hospital with lymph nodes which were infected and broken down, and in 4 others this condition developed while they were in the hospital. Elimination of an infected primary carcinoma of the penis should be rapidly done. This is generally accomplished by a cleancut operation, usually partial amputation of the penis 1 cm. beyond the carcinoma.

Two patients died of hemorrhage as the result of invasion of the femoral vessels by carcinoma. One patient died from the operation, which consisted of removal of the penis and extensive resection of the inguinal lymph nodes. This death was primarily the result of infection of the affected region, and the fact is a point in favor of control by irradiation rather than by operation.

Both operation and irradiation have to date proved impotent in dealing with metastases to the inguinal lymph nodes. Operation has probably been well done, and irradiation probably has been inadequate as to dosage and proper application. Surgical removal carries a definite mortality; irradiation, none. Early aspiration biopsy of the inguinal lymph nodes is imperative. If the lymph nodes are cancerous, a combination of external irradiation and implantation of radon seeds through an incision and under vision seems to offer the most satisfactory prognosis. Either one of these procedures alone seems to be ineffective for this type of growth. Primary external irradiation by the Coutard method, followed immediately by operative removal before dermal changes have taken place, may offer another lead toward cure.

*Hypospadias.*—Cabot,<sup>45</sup> in discussing plastic operations for hypospadias, said that, until relatively recent times, this type of deformity had not been completely overcome. Operation did not restore the affected

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45. Cabot, Hugh, in discussion on Walters, Waltman: Plastic Operations on the Genito-Urinary Tract: II. Operations on the Urethra, Proc. Staff Meet., Mayo Clin. 10:563 (Sept. 4) 1935.

parts to normal, and frequently a stricture or a fistula marred the result. There are three types of operation for the construction of the new urethra after the deformity of curvature has been corrected. The oldest of these is the so-called Thiersch-Duplay type, in which a skin flap is taken from the shaft of the penis and is therefore of thin pliable skin that does not bear hair. With experience, the results obtained with this operation are excellent, but there is risk that a fistula will form which may necessitate several operations in order to complete the work. In the Bucknall operation, fistula and stricture are avoided. The principle involved is that of turning down the penile portion against the scrotum, thereby obtaining a satisfactory flap with a broad pedicle. The objection to this procedure is that it utilizes for the floor of the urethra the tissues of the anterior portion of the scrotum, which are hair-bearing. The Ombrédanne operation has the same advantages as the Bucknall technic, although not to the same extent. It also utilizes the hair-bearing tissues of the midportion of the scrotum, and therefore it may have the same disadvantage. It is interesting to note that there is no long-time follow-up evidence in regard to the ultimate results of these operations. Most of the reports have been on patients who were followed only a relatively short time after operation, and these reports cannot be regarded as complete evidence as to success.

It is not sufficiently realized that the traumatic stricture differs essentially from the so-called inflammatory stricture, which is commonly the result of a gonorrheal infection. As compared with the inflammatory stricture, the traumatic stricture contracts early and fiercely and is exceedingly difficult to dilate. Cabot expressed the belief that the traumatic stricture, if it has not been treated skilfully and successfully by accurate reunion of the divided ends at the time of injury, should always be treated by resection and anastomosis. The important fact to consider is that there is a free and segmental blood supply of the corpus spongiosum. This structure does not resemble the corpora cavernosa by being seriously damaged if the supply of blood is interfered with at the base. The corpus spongiosum can be safely mobilized with its contained urethra to almost any extent which is necessary to make possible union between the divided ends without tension. The avoidance of tension is the crux of the procedure, and mobilizing the anterior end is the significant feature of the operation. The only other important point is that the suture should be begun on the roof. This region having been securely united, the floor of the canal should be slit, if possible, in both segments, although it is necessary to slit it only in the anterior segment, since the posterior segment will commonly be dilated. This enables union to be made, giving a canal of a caliber much in excess of the normal. When this circular scar

contracts, the ultimate result should be a canal of normal caliber. Essential features of the operation are thorough exposure, complete removal of the stricture and the surrounding scar tissues, union of the ends without tension, and provision that the canal will at the time of operation be considerably larger than normal.

#### URETHRA

*Injuries.*—Delzell and Stevens<sup>46</sup> presented a study of 37 cases of rupture of the urethra. In 7 cases the rupture involved the penile urethra; in 21, the bulbous portion; in 2, the membranous portion, and in 2, the prostatic urethra. In 7 cases the rupture was the result of injury to the penis; in 2, of a gunshot injury; in 19, of a straddle injury without pelvic fracture, and in 9, of straddle injury associated with fracture. Important diagnostic and therapeutic problems relate to prompt institution of drainage to control infection and to lessen the formation of scar tissue, early repair of the rupture when conditions permit and close observation of the patient in the hospital when the diagnosis or the procedure is in doubt. Six patients died, 1 of pneumonia twenty-five days after operation and 5 of sepsis. Three of the patients who died of infection were not seen until late.

Martin<sup>47</sup> divided injuries of the urethra into the following four classifications: (1) the so-called straddle injury, in which the membranous urethra is wholly or partially severed; (2) the classic rupture of the bladder produced by moderate impact over the organ when distended; (3) instrumental rupture of the bladder or of the posterior urethra, and (4) the injury, especially that of the posterior urethra, produced by a crushing force or a violent impact sufficient to cause fracture of the pelvis.

While the incidence of fracture of the pelvis is relatively high, only in a comparatively small percentage of the cases is the condition complicated by injury of the urethra or bladder. When such an injury is present, it is important to recognize it early and institute surgical measures for the purpose of drainage, so as to prevent further leakage into surrounding tissues. If there is any doubt as to the extent of the injury, drainage should always be instituted. In every region where urinary leakage may seem to be present or where it is even suspected to be present, adequate drainage should be provided. Unnecessary drainage leads to no serious results unless severe shock is present. If shock is excessive, it is probably the result of injuries concomitant with the urethral injury.

46. Delzell, W. R., and Stevens, A. R.: Traumatic Rupture of the Urethra: Study of Thirty-Seven Cases, *J. Urol.* **34**:372 (Nov.) 1935.

47. Martin, H. W.: Injuries of the Posterior Urethra, *J. Urol.* **34**:718 (Dec.) 1935.

The treatment consists of ample drainage of the bladder and of every region where urine may have leaked into the tissues. In many instances, infection of the urine has existed previous to the injury. Extravasation of urine invariably leads to serious infection through necrosis of the tissue. A midline abdominal incision is made over the hypogastrium. It is seldom justifiable to explore the peritoneal cavity unless there is definite evidence of injury to abdominal viscera. The bladder is opened suprapubically. The prevesical region should be examined; after opening the bladder as high up toward the retracted peritoneal fold as possible, the inner wall should be thoroughly palpated for evidence of rupture. If tears exist, better exposure may be needed. If not, a Gutierrez retrograde staff should be introduced through the suprapubic opening into the vesical neck and out through the prostatic urethra into the bulbous urethra; an incision is made in the perineum over the tip of this retrograde staff. The staff is then pushed through this button-hole opening in the perineum, and a rubber catheter or a piece of rubber tubing the size of a no. 22 French catheter is pushed well over the tip of the staff like a sleeve; it is then encircled and fastened on the staff with a silk ligature, tied securely. The staff is then withdrawn, carrying the rubber tube from the perineum into the bladder and up through the suprapubic incision in the bladder on to the skin, where it can be visualized. The rubber tube is released from the tip of the staff and is transfixed with heavy twisted silk, size 12 or 14, and the silk is knotted to form a loop. The rubber tube is then withdrawn by pulling on the portion still projecting in the perineum until the upper end is resting on the trigon, or the upper end of the tube may be sutured to the edge of the skin of the suprapubic incision. The silk loop is then fastened with a silk suture thread to the skin of the abdominal incision. A suture through the tube into the skin at one edge of the perineal wound will hold it firmly in place. A de Pezzer catheter, no. 22 French, is then sutured in place for drainage of the bladder. If there is any ecchymosis or tumefaction of the perineum, scrotum or shaft of the penis, it should be liberally incised as in any case of extravasation of urine.

*Stricture.*—Stevens<sup>48</sup> said that ectopic kidneys are not uncommon in women. The ectopia is sometimes responsible for symptoms suggestive of pathologic changes in the generative tract. Pyelography is of value in the differential diagnosis of pathologic conditions of the female generative and urinary organs. Urethral stricture occurs frequently in women. In the majority of cases it is situated at the external meatus. It may be congenital or acquired. Frequently it is

48. Stevens, W. E.: Some Observations on Female Urology, Tr. Am. A. Genito-Urin. Surgeons 28:377 (June) 1935.

responsible for pathologic changes in the upper part of the urinary tract and for a large variety of subjective symptoms, including pain in various situations. The average size of the normal urethra of the adult female is that of a no. 26 French; the average size in the presence of urethral stricture is that of a no. 21 French. Urethrograms show the *angular bend and narrowing* of the normal female urethra. Urethrography is a valuable diagnostic procedure. Frequently it is indicated in the presence of symptoms suggestive of pathologic changes in the urinary tract in this sex.

#### TESTES

*Tumors.*—Smith, Dresser and Mintz<sup>49</sup> reported a series of 100 cases of tumor of the testis the data on which were collected from a number of hospitals about Boston. The highest incidence of teratoma was in persons between the ages of 20 and 30 years; that of embryonal carcinoma was in those between 30 and 40 years. Between these two groups there was no marked difference in the rate of progress of the disease. A definite history of trauma was obtained from 13 per cent of the patients; in 5 per cent the uninvolved testis was or had been incompletely descended. There were 3 cases of bilateral tumor. Fifteen per cent of the patients were apparently well two or more years after orchidectomy. Of these, 6 had not been irradiated. In only 1 of the well patients had metastasis been noted. To the extent of the authors' knowledge, all patients who had metastatic involvement when irradiation was instituted, died of the disease or still have metastatic involvement. Only 40 per cent of the patients in this series were adequately irradiated. A standard should be established for roentgenotherapy following orchidectomy. It is necessary to irradiate the entire abdomen inasmuch as the most frequent site for metastasis is in the lumbar chain of lymph nodes. If the thorax is not included in the first series of treatments, diagnostic roentgenograms should be made every two months for at least two years.

Cutler and Owen<sup>50</sup> reported the results of quantitative determinations of the follicle-stimulating hormone in the urines of 66 patients who had teratoma of the testis. The amounts varied between 50 and 16,000 mouse units per liter. The amounts excreted in the urines of 13 normal males who had benign lesions of the testis were less than 50 mouse units per liter. The evidence supports the view that patients with teratoma of the testis excrete more than 50 mouse units per liter of urine, a fact which gives a diagnostic value to the determination of

49. Smith, G. G.; Dresser, Richard, and Mintz, E. R.: *Radiation Treatment of Tumors of the Testicle*, J. Urol. **34**:462 (Nov.) 1935.

50. Cutler, Max, and Owen, S. E.: *Clinical Value of Prolan A Determinations in Teratoma Testis*, Am. J. Cancer **24**:318 (June) 1935.

this hormone. Usually, a marked diminution in the excretion of the hormone following irradiation is accompanied by a marked regression of the disease and an improvement in the general condition of the patient; failure of the excretion to diminish or an increase following treatment is paralleled by failure to respond to therapy. Local recurrence of teratoma is often preceded by a rise in the hormone in the urine, rendering the determination of the hormone of value in the follow-up control of this group of patients. The total output of urine for twenty-four hours should be determined and taken into consideration when the quantitative determination of the hormone is made under conditions in which clinical conclusions are to be based on small variations, in order to avoid errors that might arise owing to differences in the intake of fluids. A modification of the benzoic acid method described by Katzman and Doisy is presented. This renders the test more accurate when the quantities of the excreted hormone are small, and this modification is preferable when the urine contains toxic products.

Fortner and Owen<sup>51</sup> said that chorionepithelioma rarely occurs in males, although many cases of the tumor in women have been reported. While no positive statement can be made at present concerning the origin of chorionepithelioma, there are many facts to be considered. From a study of the tumor in the female, the trophoblast is known to be normally an invasive type of tissue, and chorionic cells are reputed to possess the property of digesting the maternal tissues. The embedding of the ovum is thought to be accomplished by the aid of this characteristic. The cells of the trophoblast are endowed with marked capacity for growth. Trophoblastic emboli are said to occur in 80 per cent of normal pregnancies. This parasitic tissue, then, is able physiologically to invade and wander. The formation of chorionepitheliomatous tissue in the male has been regarded as evidence of a metaplastic change in an embryonal ectodermic structure which, under certain unrecognized conditions, is capable of producing this variety of tumorous tissue, just as these tissues may undergo carcinomatous changes in response to other stimuli.

The biologic assay of the urine for the hormone that stimulates the follicle offers the possibility of timely diagnosis. Chorionepithelioma of the testis is associated with a urinary output of this hormone varying from 10,000 to 150,000 mouse units per liter. Teratoma is also associated with an excretion of excessive amounts of this hormone in the urine, but the quantities range from 50 to 10,000 mouse units per liter, depending on the type of tumor. Since normal urine of a male

51. Fortner, H. C., and Owen, S. E.: Chorionepithelioma in the Male, *Am. J. Cancer* 25:89 (Sept.) 1935.

contains less than 50 mouse units of the hormone per liter, an increase in the amount furnishes a diagnostic test for chorionepithelioma of the testis.

Since the tumor consists of anaplastic and undifferentiated tissue, it may be expected to be highly radiosensitive. After the diagnosis has been made, preoperative irradiation may be followed by radical surgical removal of the primary growth, with subsequent postoperative irradiation to the primary site. For metastatic involvement, irradiation is at present the treatment of choice. There is a possibility that treatment of the tumor may eventually be nonsurgical, and consist in injections of serum or in endocrine gland therapy. In view of the observations made by Fraenkel, it seems that serum of pregnant animals may be beneficial. Such serums are now being utilized, but it is too early to form accurate conclusions. Owing to the close association of teratoma of the testis with chorionepithelioma, as evidenced by their endocrine relationship, it may be that the lytic agents occurring in the serum during pregnancy also affect the teratoma, a problem which is worthy of further investigation.

Two cases of chorionepithelioma of the testis are presented, with gross and microscopic illustrations. Sections from the primary tumor and from metastatic nodules disclosed in both these cases characteristics typical of chorionepithelioma. In addition to the syncytial masses dipping into large regions filled with erythrocytes, some strands appeared to have central connective tissue cores with capillaries, resembling chorionic villi. Sections through the mammary glands presented an increase in the number of acini, with an increase in the amount of fibrous tissue between them. The acini were moderately dilated and displayed evidence of activity.

Ferguson<sup>52</sup> said that a study was made in 1931 of the effect of various technics for administering a divided dosage of roentgen rays in the treatment of teratoma testis. The treatment of a series of patients with metastatic teratoma of the testis was begun as follows: The abdomen was divided into three anterior portals on the affected side. Two posterior portals were used. The groin and scrotum were treated separately. The factors used were a target skin distance of 70 cm., 200 kilovolts, 200 milliamperes, 0.5 mm. of copper and 1 mm. of aluminum. A dose of 400 roentgens was delivered to each portal in rotation on successive days. The total dose delivered in each instance was 2,000 roentgens to each skin portal. From April 1, 1932, to April 1, 1934, 25 patients were treated by this technic. During the same period, 27 patients who had the tumor were treated with roentgen

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52. Ferguson, R. S.: Selective Irradiation in the Management of Teratoma Testis, *J. Urol.* **34**:458 (Nov.) 1935.

radiation by the full erythema technic or with other agents. From the clinical standpoint each group of patients represented the average patient with teratoma of the testis seen at the hospital, and the treatment of one group was not less difficult than that of another. Of the 25 patients treated with the divided doses, 12 (48 per cent) were alive and without evidence of disease on April 1, 1935. In the other group, 10 (37 per cent) were alive and without evidence of disease for from one to three years.

The character of the growths in the patients in whom the clinical results were satisfactory was investigated. It was found that an increased percentage of growths formerly thought to be radioresistant had been observed in the patients cured with divided doses. Comparison was made with the cured patients in the series of 154 who were subjected to the full erythema doses.

The conclusion was that a further increase in the target skin distance and in filtration and a further division of the dose with the attainment of a higher total dose should be selected as the treatment of choice for the more radioresistant types of teratoma. It was also evident from the study of the series of 154 cases that intensive irradiation with less filtration and larger daily doses was preferable for the more sensitive types of the tumor. Consequently, the technic of external irradiation may be selected on the basis of the structure of the tumor and its biologic behavior. In 1933 it was shown that the biologic response of the teratoid tumor to irradiation, as measured by the quantitative assay of the urine for the follicle-stimulating hormone, is a more reliable index of the radiosensitivity of the tumor than the histologic structure alone. When the structure of the growth or its biologic response to previous treatment is known a fairly accurate prediction of radiosensitivity or resistance may be made. The patients with sensitive teratoma are now being treated by Ferguson by the 70 cm. technic, but those with more resistant teratoma are being treated by prolonged irradiation with smaller doses, greater distance and heavier filtration. Early results indicate the wisdom of this selection of treatment.

Ferguson summarized his findings as follows: The more radioresistant the tumor, the greater the necessity for more prolonged, less intense irradiation. Conversely, the more sensitive the tumor, the greater the necessity for intensive irradiation.

*Undescended Testis.*—Wangensteen<sup>53</sup> reported observations demonstrating spermatozoa in the semen after bilateral orchiopexy for failure of complete descent of the testes. He also presented proof of complete spermatogenesis in seminiferous tubules of such a testis. In pigs with

53. Wangensteen, O. H.: The Undescended Testis: Its Fate After Satisfactory Scrotal Anchorage, *Ann. Surg.* **102**:875 (Nov.) 1935.



retained testes which could be brought into the scrotum by orchiopexy, spermatogenesis was also demonstrated. It is apparent, however, in human beings as well as in pigs in which this deformity has been corrected, that satisfactory scrotal anchorage does not permit a uniform and diffuse restoration of mature germinal epithelium such as attends scrotal transference of the normal (dog's) testis, temporarily elevated from the scrotum to the abdomen.

Whereas these results scarcely justify a stockbreeder in having bilateral orchiopexy performed, for breeding purposes, on an animal with a valuable pedigree, the virtue of orchiopexy in rectifying the sterility of cryptorchides warrants the performance of the operation in man in all suitable cases in which the condition is bilateral. Apart from the consideration of sterility, which does not concern unilateral failure of descent, the same indications which determine the necessity for operation in cases of bilateral undescended testis should be applied in cases of unilateral retention of the testis.

Pace<sup>54</sup> examined 24 specimens of unilateral undescended testis from adults. These organs had been removed surgically within the past thirty-two years at the Mayo Clinic. Seven of the specimens had been situated in the right inguinal canal; 7, in the left inguinal canal; 4, at the left external abdominal ring; 2, at the right external abdominal ring, and 3, within the abdomen, 2 on the left side and 1 on the right. Twenty-two of these undescended testes were associated with inguinal hernias. Two patients were in the second decade of life; 6, in the third decade; 5, in the fourth decade; 4, in the fifth decade; 2, in the sixth decade, and 5, in the seventh decade. One of the 2 testes obtained from patients in the second decade of life contained tubules which were not devoid of germinal epithelium and might have produced a mature germinal epithelium if placed in the scrotum. The testis of the other patient in this decade of life contained only remnants of testicular tissue and probably was grossly undeveloped. Each of the 6 specimens from patients in the third decade of life revealed some evidence of atrophy of the germinal epithelium; in each instance the remaining epithelium was in a fair state of preservation and might have given evidence of regeneration if the testis had been placed in its normal position. After histologic study of the 5 specimens obtained from patients in the fourth decade of life, it appeared that 4 might have been able to produce a mature germinal epithelium if they had been placed in the scrotum. Of the 4 specimens from patients in the fifth decade, the epithelium in 2 might have functioned had the testes been placed in the scrotum. In 1 of the 2 patients in the sixth decade of life, the

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54. Pace, J. M.: The Histologic and Pathologic Anatomy of the Retained Testis, *Proc. Staff Meet., Mayo Clin.* 10:726 (Nov. 13) 1935.

testicular tissue was replaced completely by fibrous connective tissue. In the other, the tubules were largely fibrosed and replaced with hyalin. In the testes of 4 of the 5 patients in the seventh decade of life, the tubules showed fibrosis and hyalinization of varying degrees. From this study it seems that the 13 testes from patients in the first four decades of life and at least 1 from a patient in the fifth decade might have been able to produce a mature germinal epithelium if the organs had been placed in the scrotum, and that atrophy and degeneration of the testicular tubules progress with age in the undescended testis.

MacCarty<sup>55</sup> said that tumor of intra-abdominal undescended testes is rare. Only a few cases have been noted at the Mayo Clinic, and a small number have been presented in the literature. Undescended testes are rather common. Tumor of descended testes occurs comparatively frequently. In view of these facts MacCarty has been conservative in advice as to the procedure in an uncomplicated case of intra-abdominal testis. It should not be removed simply because of its position, although it might rarely become malignant. The inguinal testis is more liable to injury, and injury as a frequent stimulus to the production of a neoplasm in any place in the body can never be ignored.

Cabot<sup>56</sup> said that the conclusions as to the possibility of regeneration of the tubular portions of the testis following its placement in a normal position are based almost entirely on animal experimentation. These experiments suggest that extensive degeneration of the tubular epithelium may take place and yet be followed by a practically complete restoration to normal if the testis is again placed in a normal position. Such observations are significant not only in the management of undescended testis in a child but also in the advising of the adult patient. Pace's studies appear to show that degeneration and hyalinization of the tubules are slowly progressive; he further suggests that at least in his series the degeneration and hyalinization are not complete until the fifth decade of life or even later. From this it appears that replacement of the undescended testis should be advised for the adult patient at least up to his fortieth year. The observations also discourage the habit of performing orchidectomy on rather incomplete evidence.

#### SPERMATIC CORD

*Division.*—Burdick and Higinbotham<sup>57</sup> have practiced complete division of all the structures comprising the spermatic cord as an aid in the cure of certain types of inguinal hernia. In some cases it was

55. MacCarty, W. C., in discussion on Pace,<sup>54</sup> p. 728.

56. Cabot, Hugh, in discussion on Pace,<sup>54</sup> p. 729.

57. Burdick, C. G., and Higinbotham, N. L.: Division of the Spermatic Cord as an Aid in Operating on Selected Types of Inguinal Hernia, *Ann. Surg.* **102**:863 (Nov.) 1935.

observed at operation that the vessels had been practically destroyed without necrosis of the testis. The spermatic cord was intentionally divided, and it was found that the testis did not slough. The indications for this radical procedure are: recurrence of hernia in a patient more than 50 years of age in whom there have been one or more unsuccessful attempts at a radical cure and in whom the opposite testis is apparently normal; recurrence of hernia in a younger man who is incapacitated for his usual occupation and who has an apparently normal testis on the opposite side; large scrotal hernia in an aged person which is either irreducible or cannot be satisfactorily retained by a truss, and large sliding hernia.

In order to obtain the maximal benefit in saving time, the spermatic cord must be divided early in the operation. A ligature is placed about the cord at the point where it emerges from the internal abdominal ring, and a second one is placed at the point where it enters the scrotum; the intervening tissue is excised. There is always considerable swelling, accompanied by redness of the skin and edema of the scrotum. In some of their cases, gangrene seemed imminent and in 4 of these cases it occurred. The patient is kept in bed for the usual time, depending on the type of hernia, and is advised to wear a suspensory until the swelling has entirely subsided.

Complete division of the spermatic cord had been used in the repair of inguinal hernia in 200 patients. The cord was divided on one side in 166 of the patients, and in 17 the hernia was repaired and the cord was divided on both sides. Nine patients died; 6 (3.2 per cent), in consequence of the operation; 1, of pneumonia three and a half years after operation; 1, of a fractured skull following an accident sixteen months after operation, and 1, of heart disease two years after operation. Of the wounds, 159 healed by primary union, 6 were drained at the lower angle at the time of operation and healed in from ten to thirty days, while 33 (17.5 per cent) became infected.

Of 169 patients on whom there were follow-up records, the condition of the testis was noted in only 79. A common observation was moderate swelling of the testis for one or two months after operation, followed by diminution in the swelling and return to normal; atrophy of the testis occurred in some of these patients. In one the testis remained swollen for six months, and in another, for a year. The testis was recorded as normal in size in 42 patients; 25 of these patients were followed for from one to five years. All patients who were subjected to bilateral division of the spermatic cord were found to have testes of normal size. Of the remaining patients, 11 had slight atrophy of the testis, and 11 others had atrophy to a half or less of the normal size. Of the 169 patients who returned for one or more examinations,

20 had recurrence of hernia; in 1 patient the hernia recurred as early as one month after operation, and in another, as late as thirty-nine months; the average interval between operation and recurrence was nine and five-tenths months.

*Torsion.*—Kinney<sup>58</sup> reported a case of torsion of the spermatic cord. About 250 cases of torsion of the spermatic cord have been reported in the literature. In many instances, atrophy of the testis unquestionably is the result of previous torsion of the cord. Early diagnosis is imperative, and in the majority of cases detorsion can be satisfactorily accomplished only if the patient is seen within an hour or so after torsion has occurred. Even if detorsion can be performed, atrophy of the testis usually occurs. Torsion of the cord can occur at any age but it occurs most frequently in adolescence. The etiology is of little significance in the prevention, diagnosis and treatment of this condition. The right spermatic cord and testis are involved in the ratio of about 3:2. The Prehn sign seems to be of definite value in the differential diagnosis of epididymitis and torsion of the spermatic cord. The treatment should be surgical, and an appeal is made for prophylactic treatment and for the inspection of the opposite side in all cases of torsion of the spermatic cord.

#### SCROTUM

*Congenital Canals and Cysts.*—Neff<sup>59</sup> reported 5 cases of congenital canals or cysts of the genitoperineal raphe and 1 case of a periurethral cyst. These canals and cysts are said to arise from epithelial rests incident to imperfect ventral fusion in the formation of the external genitalia or from masses of epithelial cells which have migrated from the primitive epithelium. The cysts and canals are therefore congenital. They have an epidermoid or mucous lining, depending on their cells of origin. The lining of the canals is almost invariably epidermoid; a smaller majority of the cysts show this type of lining. The canals of the raphe apparently manifest themselves only after infection, usually after gonorrheal infection. The canals may become infected without involvement of the urethra. The treatment of both canals and cysts is surgical.

#### URINE

*Diversion of Urinary Stream.*—Cabot and Scherer<sup>60</sup> said that extrophy of the bladder is the most outstanding of the congenital

58. Kinney, W. H.: *Torsion of the Spermatic Cord*, J. Urol. **34**:470 (Nov.) 1935.

59. Neff, J. H.: *Congenital Canals and Cysts of the Genito-Perineal Raphe*, Tr. Am. A. Genito-Urin. Surgeons **28**:415 (June) 1935.

60. Cabot, Hugh, and Scherer, R. G.: *Choice of Methods of Diverting the Urinary Stream Above the Level of the Bladder*, Ann. Surg. **102**:849 (Nov.) 1935.

anomalies for which diversion of the urinary stream above the level of the bladder may be necessary. Closely allied to this condition is the severe grade of epispadias, which may be defined as a situation in which the superior wall of the urethra is missing together with the sphincteric mechanism of the neck of the bladder. A third type of anomaly suitable for this procedure is an undefined condition in which there apparently is some congenital defect in the nerve mechanism controlling the musculature of the urinary tract. Diversion of the urinary stream may be indicated for certain injuries of the bladder or ureters. This statement includes the unusually large vesicovaginal fistula, often in cases in which several attempts at operative cure have failed. When the stage is reached at which there is insufficient tissue with which to construct a satisfactory floor of the bladder, diversion of the urine above that level must be considered. Injury of one or both ureters occasionally occurs in pelvic operations, most commonly in operations for cancer. Inflammatory (nontuberculous) cystitis is another condition for which this procedure is suitable. Cabot and Scherer were of the opinion that, although the latter condition may be described by a variety of names, it really is an extensive chronic interstitial cystitis. Another suitable condition is tuberculous cystitis, usually secondary to renal tuberculosis. At the outset the diagnosis of unilateral surgical tuberculosis may have been satisfactorily made and nephrectomy done. Sometimes, the tuberculous cystitis never subsides sufficiently to allow reasonable comfort. In this group of cases of cystitis resulting from tuberculosis and in the preceding one of cases of nontuberculous origin drainage of the bladder by suprapubic cystostomy fails to give satisfactory relief. It is further significant that when nephrectomy has been performed for tuberculosis, the ureter of the remaining kidney is frequently abnormal and often reveals considerable dilation, apparently the result of an increased thickness of the wall of the bladder caused by hypertrophy produced by frequency of urination. For this condition cystostomy will not be satisfactory. Finally, there is the relatively large group of cases of cancer of the bladder in which the growth encroaches or will encroach on one or both ureters and in which the satisfactory removal or destruction of the tumor will fail to relieve the patient. For those of these lesions in which resection of the wall of the bladder is considered advisable, reimplantation of the ureter offers a satisfactory solution.

There are three methods of diverting the urinary stream: nephrostomy, uretero-enterostomy and cutaneous ureterostomy. Since nephrostomy, except for temporary diversion of the urine, is preferred to pyelostomy, the latter method is not discussed. Nephrostomy diverts the urine at the level of the kidney. Its advantage over other methods is that it does not involve the division of the ureter. It may, therefore,

be employed as an intermediate stage, when, owing to conditions, such as the proximity of a recent serious abdominal operation, no rearrangement of the ureter can properly be undertaken. Entero-anastomosis has gained in favor since the technic suggested by Coffey, that is, oblique introduction of the ureter into the bowel, began to be generally used. This operation is technically difficult and requires familiarity with the surgery of the urinary, as well as of the intestinal, tract. The outstanding danger is that of infection either in connection with the operation or at various subsequent periods, owing to an ascending ureteritis and pyelonephritis which have previously been subject to periodic exacerbations. Cutaneous ureterostomy was first undertaken many years ago. Like uretero-enterostomy, it involves complete separation of the ureter from the bladder, and to this extent is permanent. It is technically a simple operation as compared with uretero-enterostomy, and the drainage is good if properly managed. The danger of infection is probably no more than that involved in intestinal anastomosis, and should a severe infection occur, the ureter is accessible for irrigation and drainage. It is particularly applicable to the abnormal ureter, which is more readily managed by this technic than is the normal one.

Nephrostomy is perhaps at its best as a temporary expedient until a more permanent arrangement, such as reimplantation of the ureter into the bladder, possibly uretero-ureteral anastomosis or uretero-intestinal anastomosis, may be performed. The patients most favorable for uretero-enterostomy are children who have exstrophy or epispadias and whose ureters are normal. The operative mortality for these patients, provided the appropriate technic is used, should be less than 5 per cent. The next most suitable group will be patients whose bladders are seriously involved but whose ureters have remained normal. Cutaneous ureterostomy is the method of election for the majority of patients whose ureters are grossly abnormal. This is particularly the choice for patients with vesical tuberculosis of an intolerable and intractable type, whether the condition is bilateral inoperable tuberculosis of the kidney, tuberculosis of a remaining kidney after nephrectomy or an intractable lesion of the bladder with the condition of the remaining kidney normal except for some dilation and atony of the ureter. For these patients relief may be expected. The duration of life will depend on the condition of the kidneys as concerns infection with tuberculosis.

*Essential Hematuria.*—Colella<sup>61</sup> concluded, after an intensive study of 10 cases of hematuria and an exhaustive review of the literature,

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61. Colella, P. R.: Sul meccanismo di azione della decapsulazione e risultati prossimi e remoti della stessa nella cura della nefrite emorragica, *Arch. ital. di urol.* 12:695 (July) 1935.

that in evaluating the results of decapsulation of the kidney a clearcut distinction must be made between the cases of essential hematuria, which he calls "hemorrhagic nephritis," and cases of hematuria in which the condition must be regarded as the expression of a definitely inflammatory condition (nephropylitis or pyelonephritis with hemorrhagic manifestations). While it is true that this conception of "essential hematuria" as an entity is accepted only with reluctance by the majority of urologists, the need of differentiating between this condition and hematuria in which the bleeding is clearly inflammatory in origin has recently been discussed by Heitz-Boyer and others in the *Société Française d'Urologie* in terms that it is impossible to ignore. Although from the point of view of pathogenesis and symptomatology the inflammatory forms of renal hemorrhage and the forms of simple hematuric nephritis are scarcely distinguishable, owing to the difficulty of determining the cause of the hematuria, this distinction must definitely be made with reference to the form of treatment to be employed in order not to discredit the true value of decapsulation when applied with discrimination in suitable cases.

Colella reported 10 cases in which he carried out decapsulation. In 9 of these the results were just what he had hoped for, and the hematuria came promptly to an end. In the tenth case decapsulation had no effect because the patient was suffering from acute and chronic lesions of pyelonephritis accompanied by hemorrhagic manifestations; in this case, nephrectomy was necessary to stop the bleeding.

Colella concluded that decapsulation acts on the supply of intrarenal blood by a mechanism that is chiefly nervous and of a vasodilating nature. Hence it follows that this procedure is justifiable only in cases in which an increase of pressure, caused by vasoconstriction, may set up a sudden disequilibrium of the circulation with consequent obstruction of the free outflow of blood—a disequilibrium which, as it increases through the persistence of nervous stimuli, not well defined and perhaps toxic, paves the way for hemorrhagic phenomena as time goes on. The general conception is that the decapsulated kidney permits the passage of a greater amount of blood in a given time or that it has a better blood supply than does the nondecapsulated one. Since the number of afferent vessels is unchanged, it follows that the increased supply of blood is referable to an increased velocity of circulation within the kidney or to a greater fulness of its vascular bed; in other words, to vasodilatation, with diminution of intramural circulatory resistance, especially within the capillaries. This is the argument for the value of the procedure in essential hematuria.

In conditions that are clearly inflammatory (pyelonephritis) hyperemia is already present, in the conception of inflammation, and if

to this there is superadded a special exalted toxic and pathogenic power of the bacteria and their toxins hematuria may be the result not only of a more rapid and sudden vasodilator congestion but also of lesions of the walls of the vessels. Histologic observations bear out this assertion and explain why decapsulation in such a case gives results that are either transitory or entirely negative, as in Colella's tenth case. In cases of essential hematuria, however, he is of the opinion that decapsulation is the method of choice to stop the hemorrhage, for he believes that it gives lasting results in a high percentage of the cases.

*Pyuria.*—Hepler<sup>62</sup> said that within recent years there has been a growing recognition of the importance of a complete urologic examination of the infant when there is presumptive evidence of disease of the urinary tract. This increasing application of modern diagnostic methods to urologic conditions in children has established a number of facts, the most significant of which are that congenital narrowing of the caliber of the urinary tract, chiefly at the points of normal anatomic narrowing, is common, and that congenital obstruction is an important factor in urinary diseases both in children and in adults; chronic infections are usually secondary to or are perpetuated by these obstructions, and chronic or recurrent pyuria almost invariably indicates some anatomic defect; further, disease of the urinary tract among children is often obscured by symptoms pointing to other conditions, frequently gastro-intestinal disorders.

Infants and children do not localize their subjective symptoms, and many of the lesions do not produce symptoms. Pyuria is the most significant sign of urogenital disease in children.

From a study of 694 infants and children during a period of nine months at the Children's Orthopedic Hospital, Seattle, it was concluded that catheterization is necessary in the diagnosis of urinary disease in children. Ninety-nine per cent of 692 patients had pus in the voided urine, and only 13 per cent had pus in the catheterized specimen. The amount of pus in urine which is properly collected is no indication either of the kind or of the severity of the disease of the urinary tract. In the 24 patients in whom there was demonstrable disease of the urinary tract exactly similar lesions existed, and the number of pus cells in the urine varied from less than 1 to more than 20 per high-power dry field. Fifty per cent of the children who had demonstrable disease of the urinary tract, including a number who had advanced lesions and severe infections, had fewer pus cells in the urine than the number which is frequently established as normal. If a persistent or recurrent pyuria, regardless of the number of pus cells, is taken as a criterion for a com-

62. Hepler, A. B., and Scott, R. T.: The Significance of Pyuria in Children, J. A. M. A. **105**:499 (Aug. 17) 1935.



plete renal study, a number of children will be subjected to what is apparently an unnecessary examination, for only 37 per cent of the 64 who had pus cells in the catheterized specimen had demonstrable disease of the urinary tract. Only 9 of the 26 children in the study who had disease of the urinary tract had subjective symptoms that were referable to the urinary tract. Urinary complications in children who have tuberculosis of the bones and joints are not common, and prolonged immobilization on frames or in casts does not tend to produce urinary stasis, infection or formation of stones. Forty-one of the children examined had tuberculosis of bones or joints. Tubercle bacilli were not found in the urine after repeated and careful examinations. Only 7 had pus in the urine, and none of these had any demonstrable disease of the urinary tract.

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## CHRONIC THYROIDITIS

A COMPARATIVE ANALYSIS OF ONE HUNDRED CASES

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Growing interest of late in the function of the thyroid gland and its relationship to endocrine disorders has so aroused interest in pathologic processes involving the gland that I was prompted to translate from the German an original paper dealing with one hundred cases of chronic inflammation of this gland.

The cases under discussion formed the basis for a thesis prepared under the personal supervision of Prof. Dr. F. de Quervain, director of the surgical clinic at the University of Bern, Switzerland, who will vouch both for the accuracy of all figures and for all statements quoted in the text.

The material which Prof. de Quervain placed at my disposal comprises one hundred cases of chronic inflammation of the thyroid gland. Seventy-seven of the patients were seen at the surgical clinic of the University of Bern and represent all such patients seen and operated on in that institution for a period of sixteen years (1918-1933). The remaining twenty-three were seen at the Sanatorium Victoria, likewise located in Bern, and under the direction of Prof. de Quervain. They, too, represent all patients with chronic thyroiditis admitted for treatment and operation from 1918 until 1933, inclusive.

In each case the histologic diagnosis was made by Prof. Dr. C. Wegelin, director of the pathologic institute of the University of Bern.

The entire group of persons with goiter treated at the University of Bern and the Sanatorium Victoria from 1918 to 1933 total 4,148. The types of thyroiditis were distributed as follows:

Type	No. of Cases
Genuine exophthalmic goiter.....	128
Exophthalmic goiter induced by iodine.....	185
Chronic strumitis (nonsuppurative).....	97
Chronic strumitis (suppurative).....	3
Acute strumitis (nonsuppurative).....	22
Acute strumitis (suppurative).....	9
Tuberculosis of the thyroid gland.....	10
Syphilis of the thyroid gland.....	2
Struma maligna.....	131

Up to the present time, most discussions on chronic thyroiditis have been limited to that of a specific nature, such as tuberculosis or syphilis of the thyroid gland (Ast, Davis, Dimtza,<sup>1</sup> Petersen, Rendelmann and Marker, Riedel<sup>2</sup>).

An additional form embraces the condition known as chronic non-specific thyroiditis, or the so-called "iron-hard" strumitis of Riedel, which because of its peculiar clinical symptomatology and histologic picture earns special consideration in a study of pathologic processes involving the thyroid gland. More than seventy publications dealing with this rare and remarkable disease of the thyroid have already appeared in the literature, some of which are those by Crane, Heinke, Kent, Maloney, Reist, Riedel, Smith and Clute.<sup>3</sup>

This discussion deals with one hundred cases of chronic inflammation of the thyroid gland of a nonspecific nature.

#### CLINICAL SYMPTOMS

Chronic inflammation of the thyroid gland is an infrequent clinical malady recognizable only postoperatively by means of histologic investigation. Discovery of the illness can be said to be accidental, as the clinical symptoms prior to operation do not warrant consideration of a diagnosis of chronic inflammation.

In relation to clinical form, I should like, therefore, to divide the one hundred cases into three distinct groups.

*Group 1.*—The first group consists of sixty-six cases in which there are no clinical symptoms of inflammation. Most of the patients in this group were operated on because of the customary symptoms and history of an ordinary struma. Subjective complaints were confined to slight dyspnea. In the vast majority of cases there was firm and nodular enlargement of the thyroid gland. In fifty-eight cases the patient gave a history of prevalent goiter of many years' standing.

1. Dimtza, Alexander: Zur Tuberkulose der Struma, Zurich, 1930.

2. Riedel, B. M. C. L.: Ueber Verlauf und Ausgang der Strumitis chronica, München. med. Wchnschr. **57**: 1946, 1910.

3. Crane, Whitefield: Chronic Thyroiditis, California & West. Med. **35**:443-446, 1931. Heinke: Die chronische Thyreoiditis, Deutsche Ztschr. f. Chir. **56**: 2566-2570 (Oct. 12) 1929. Kent, George B.: Riedel's Chronic Thyroiditis, Colorado Med. **26**:132-139 (May) 1929. Maloney, John J.: Ligneous Thyroiditis (Riedel's Disease), J. Med. **10**:586-589 (Feb.) 1930. Reist, A.: Ueber chronische Thyreoiditis, Frankfurt. Ztschr. f. Path. **28**:141-200, 1922. Riedel, B. M. C. L.: Die chronische, zur Bildung eisenharter Tumoren führende Entzündung der Schilddrüse, Verhandl. d. deutsch. Gesellsch. f. Chir. **25**:101, 1896; Vorstellung eines Kranken mit chronischer Strumitis, *ibid.* **26**:127, 1897; footnote 2. Smith, L. W., and Clute, H. M.: Chronic Ligneous Thyroiditis (Riedel's Struma), Am. J. M. Sc. **172**:403-416 (Sept.) 1926.

*Group 2.*—The second group consists of nineteen cases in which there were no clinical symptoms of inflammation. All the patients in this group presented clinical symptoms which showed deviations from ordinary enlargement of the thyroid gland and aroused suspicion of inflammation. Such symptoms were, above all, swelling, tenderness and pain, both local on pressure and of a radiating nature. Dyspnea and dysphagia were common but were observed only in mild degree. The form of enlargement of the thyroid gland in this group was decidedly diffuse.

TABLE 1.—*Relative Frequency of the Various Clinical Symptoms*

Clinical Symptom	Group 1 (66 Cases)	Group 2 (19 Cases)	Group 3 (15 Cases)
Swelling.....	..	10	3
Pain.....	..	8	..
Dyspnea.....	23	6	3
Dysphagia.....	2	2	..
Hoarseness.....	..	..	..
Symptoms of exophthalmic goiter.....	..	..	15
Symptoms of exophthalmic goiter (Basedow)...	..	..	15
Tachycardia.....	..	..	6
Tremor.....	..	..	2
Exophthalmos.....	..	..	2
Increase in basal metabolism.....	..	..	4
Previous history of goiter.....	53	14	9

TABLE 2.—*Relationship Between Clinical Course and Various Forms of Enlargement of the Thyroid Gland*

	Diffuse Struma (11 Cases)	Diffuse and Nodular Struma (16 Cases)	Nodular Struma (71 Cases)	Atrophy of the Thyroid Tissue (2 Cases)
Group 1: 66 cases without clinical symptoms of inflammation .....	1 (1.6%)	7 (11.6%)	56 (84%)	2
Group 2: 19 cases with clinical symptoms of inflammation .....	7 (36.8%)	4 (21%)	8 (42%)	..
Group 3: 15 cases of the hyperthyrotic form....	3 (20%)	5 (33%)	7 (46%)	..

*Group 3.*—The third group, consisting of fifteen cases, is designated as the hyperthyrotic group. Here are encountered all grades of exophthalmic goiter from slight to an average size. The increase in the basal metabolic rate in each instance was reported to lie between the limits of +18 and +48. Several patients complained of palpitation, loss of weight and tremor. Exophthalmos of medium grade was observed in two cases. A history of goiter at some previous time was given by nine patients (60 per cent). The form of enlargement of the thyroid gland was principally of the nodular type.

From table 2 it is seen that the adenomatous or nodular form of enlargement of the thyroid gland occurs chiefly in those persons who show the fewest symptoms of inflammation prior to operation.

## ETIOLOGY

It is assumed that the actual cause of chronic thyroiditis is a bacterial-toxic one. At any rate that is the impression one gains from a survey of the current literature on the subject. Definite evidence of such an etiology, however, has been forthcoming only in cases of chronic inflammation of a specific nature, despite the fact that the presence of tubercle bacilli or spirochetes themselves has seldom been demonstrated in the thyroid gland.

In the material studied, considerable evidence was found which pointed toward a bacterial cause. An analysis of the past histories of the patients showed that fourteen gave evidence of an infectious disease having preceded the chronic enlargement of the thyroid gland. The distribution was as follows: grip, in seven cases; bronchitis, in two; typhoid, in one; measles, in one; acute appendicitis, in two, and angina, in one. It is noteworthy that in several instances the illness occurred a number of years previous to the involvement of the thyroid gland.

At first glance these figures would appear not to substantiate the claim of a bacterial-toxic causal factor. They are somewhat misleading, by reason of the fact that other preceding illnesses enter into consideration which were usually not included or gone into with any degree of thoroughness and therefore were omitted from the case histories, especially the inflammatory diseases of the gastro-intestinal tract (de Quervain<sup>4</sup> and Kocher<sup>5</sup>). Further, there are fourteen cases in which the chronic inflammation could be traced back to a toxic origin. These patients had all been taking therapeutic doses of iodine over a period of several years.

A discussion of the etiology of chronic thyroiditis must include first the problem of predisposition. An analysis of the cases shows such a predisposition to be present as regards both sex and age.

In the division of the patients according to sex, the females were strongly predominant. Of the total number of patients, eighty-five are women (85 per cent) and fifteen men (15 per cent). Kocher<sup>5</sup> and de Quervain<sup>4</sup> expressed the opinion that the frequently existing condition of reflex hyperemia of the thyroid gland in the female sex (menses, gravidity and menopause) enters into consideration as a predisposing factor for chronic thyroiditis.

In reference to age, many previous observers have been impressed with the fact that persons in the early years of childhood and in the late years of adult life are spared and that during these years the thyroid gland is not susceptible to inflammation (de Quervain<sup>4</sup>). Table 3 shows

4. de Quervain, F.: Die akute, nicht eiterige Thyreoiditis, Mitt. a. d. Grenzgeb. d. Med. u. Chir. (supp.) 2:1-165, 1904.

5. Kocher, cited by de Quervain.<sup>4</sup>

the distribution of the patients according to age in the one hundred cases studied.

Of paramount importance is the question of the predisposing rôle played by previously existing goiter in the development of chronic inflammation of the thyroid gland. All authors are in agreement that the normal functioning and healthy thyroid gland falls prey to inflammatory processes far more seldom than does the gland showing nodular degeneration. The theories advanced to substantiate this claim are that in the latter either the glandular secretion of the thyroid has become weakened, has lost its normal power of immunity and can no longer kill invading bacteria or that the normal resistance of the organ to generalized infection has been lowered.

According to Kocher,<sup>5</sup> goiter should be regarded as prerequisite for strumitis or thyroiditis.

De Quervain<sup>4</sup> expressed the opinion that the nodular form of enlargement of the thyroid gland is especially amenable to the settlement of bacteria which produce inflammatory lesions, first because of

TABLE 3.—*Distribution of Patients According to Age*

	Age						
	0-9	10-19	20-29	30-39	40-49	50-59	60-69
Number of Patients.....	..	21	19	24	20	15	1

the necrosis of the tissue which often takes place in these nodules and secondly because of the frequent occurrence of spontaneous bleeding. According to this author, even a lesser change in the thyroid gland, such as slight diffuse hypertrophy, can cause a predisposition to inflammation of the gland.

In the material studied here, 76 per cent of the patients presented a history of previous enlargement of the thyroid gland. Although this percentage might seem high, it actually represents a most conservative estimate. In regions in which endemic goiter is prevalent, like the Swiss Jura, where goiter is a common sight on the city streets, many persons with diffuse enlargement of the thyroid gland are regarded as having merely a somewhat "thick neck." Again, it is common knowledge that small adenomas readily escape observation by most of their carriers.

Trauma has also been considered by several authors in the past as a predisposing factor. In two of the one hundred cases, indirect trauma followed by slight bleeding directly preceded the involvement of the thyroid gland. In one the swelling occurred soon after strenuous and continuous vocal effort; in the other it followed an attempt at strangulation.

Kocher mentioned that even the simple puncture of the thyroid gland may be considered to reduce its resistance to infection so as to make it readily amenable to inflammation. A similar condition was observed in the group of one hundred patients under consideration.

#### CLINICAL DIAGNOSIS

The inflammatory nature of this condition is difficult to diagnose clinically in patients who show no symptoms or few. Often clinical symptoms of sufficient intensity might lead one to entertain a diagnosis of inflammation. The symptoms, however, are never dominant. Such a diagnosis is based merely on presumption and has no foundation in fact. Diagnosis of chronic inflammation can be substantiated only by means of histologic examination.

In several cases such symptoms as a rapid increase of growth and radiating pain were suggestive of struma maligna. A more exacting inspection, however, proved that the true signs of malignancy, such as immobility and hard consistency, were lacking, so that a diagnosis of struma maligna could not be entertained in any one of the cases under consideration.

Of importance is the differentiation between thyroiditis and strumitis. The answer to this problem must of necessity remain a diagnostic enigma in view of the fact that the clinical report offers no evidence by which to distinguish one condition from the other. Differential diagnosis is rendered yet more difficult when it is considered that thyroiditis is seen not only in normal and diffusely enlarged glands but in nodular glands.

The current literature, to a certain degree, is still not clear as to the distinction between thyroiditis and strumitis. Eberts and Fitzgerald,<sup>6</sup> as well as many contemporary authors, stated that an inflammatory lesion of the thyroid gland may develop in either a normal or a goitrous gland. If it develops in a normal gland, the lesion is called thyroiditis; if in a goitrous gland, strumitis.

According to Wegelin,<sup>7</sup> thyroiditis can also occur in a goitrous gland and is to be denoted as such when the inflammation is confined solely to the remaining normal or diffusely enlarged glandular tissue and the nodules remain untouched. On the other hand, those cases in which the inflammatory process is limited to or is present mainly in the adenomatous nodules are to be considered as strumitis. From these statements, one can see that the possibility of meeting combined forms of

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6. Eberts, E. M., and Fitzgerald, R. R.: *Inflammatory Lesions of the Thyroid Gland*, *Canad. M. A. J.* **17**:1005-1009 (Sept.) 1927.

7. Wegelin, C.: "Schilddrüse," in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1928, vol. 8, p. 1.

strumitis and thyroiditis must be reckoned with. Table 4 presents a summary of the proportion of thyroiditis and strumitis among the different forms of enlargement of the thyroid gland in the one hundred cases studied.

#### PROGNOSIS AND THERAPY

The prognosis in all cases here discussed was considered good. Complications developed in three cases in the form of suppuration and formation of a fistula. However, even in such cases the prognosis can be viewed as more favorable than in cases of acute suppurative thyroiditis or strumitis. In reference to therapy, strumectomy in the form of partial resection was indicated and carried out in all instances: in forty-three cases, on the right lobe; in seventeen, on the left lobe, and in forty cases, on both the right and the left lobe. Recovery in all cases was complete.

TABLE 4.—*Relationship Between Form of Inflammation and Form of Enlargement*

Form of Inflammation	Diffuse Struma (11 Cases)	Diffuse and Nodular Struma (16 Cases)	Nodular Struma (71 Cases)	Atrophy of Thyroid Tissue (2 Cases)
Thyroiditis (37 cases).....	9	5	21	2
Thyroiditis and strumitis (7 cases).....	..	1	6	..
Strumitis (56 cases).....	2	10	44	..

#### PATHOLOGICO-ANATOMIC CHANGES

As regards the results of the histologic examinations, the inflammatory infiltrate will be considered first. In the material studied, the round cell infiltration consisted of lymphocytes, plasma cells, leukocytes and giant cells.

Lymphocytes were seen in every one of the one hundred glands under observation. They were therefore present in 100 per cent of the cases studied. Plasma cells appeared less frequently (53 per cent).

It is of special importance to note that both the lymphocytes and the plasma cells appeared principally interstitially and only seldom penetrated into the lumen of the acini. On the other hand, the appearance of foreign body giant cells in the acini was observed in thirteen of the preparations (13 per cent), although this form of cell was found to occur interstitially in many specimens.

The function of these giant cells appears to be that of removing the almost insoluble and concentrated colloid masses. This concurs with the observations made on the material studied. Giant cells approaching the diameter of middle-sized follicles were found in considerable numbers lying either between the separate nodules or in the center of the acini. The central portion of these cells was filled with basophilic masses of colloid.



Despite their similarity to leukocytes, several authors consider these cells as originating from the interfollicular epithelium, while de Quervain expressed the opinion that they are of inflammatory origin. According to this author, these foreign body giant cells show a certain similarity to the giant cells found in the tubercle in cases of tuberculosis.

The eosinophils were seen in the infiltrate in forty-eight cases (48 per cent), chiefly in the interstitial tissue.

The appearance of an occasional neutrophil was noted in fifteen cases (15 per cent).

Lymphoid follicles were observed in but three (3 per cent) of the histologic sections under observation.

Table 5 shows that the percentage of participation of the various cell forms in the infiltrate is approximately the same for the different forms of enlargement of the thyroid gland.

TABLE 5.—*Relative Frequency of the Different Cell Forms in the Infiltrate*

Cell Forms Present	Diffuse Struma (11 Cases)	Diffuse and Nodular Struma (16 Cases)	Nodular Struma (71 Cases)	Total (100 Cases)*
Lymphocytes.....	11 (100%)	16 (100%)	71 (100%)	100%
Plasma cells.....	7 (64%)	7 (43%)	33 (53%)	52%
Eosinophils.....	5 (45%)	8 (50%)	35 (50%)	48%
Neutrophils.....	2 (18%)	3 (19%)	9 (12.5%)	13%
Giant cells.....	1 (9%)	3 (19%)	9 (12.5%)	13%
Lymphoid follicles.....	1 (9%)	.....	2 (2.8%)	3%

\* This total includes two cases of atrophy of the thyroid gland.

As a direct result of the inflammation, there is a decided increase in the formation of connective tissue and a hyaline degeneration of the same in seventy-four cases (74 per cent). The increase in the formation of connective tissue appears to follow in the wake of the inflammatory infiltrate. In the vast majority of cases it seems that this increase in the formation of connective tissue takes its origin from the intralobular stroma. In others, the widening of the septums of connective tissue between the lobules is more striking. It is possible that the broadening of these interlobular septums results from apposition of connective tissue which has its origin in those lobules that have been replaced by fibrous tissue. Like the inflammatory infiltrate, the fibrous connective tissue appears in irregular mass form in the intralobular stroma, but it is equally and diffusely distributed in the interlobular stroma.

Parallel to the regressive changes in the connective tissue, degenerative and atrophic processes take place in the parenchyma. On the other hand, several reparative processes take place in the glandular parenchyma (papillae, cushion building, etc.).

In the cases studied here it was possible to observe the aforementioned degenerative and reparative processes in various stages of advancement. In some cases it was possible to view different phases of a degenerative nature in the same preparation. Thus, there were places where near a group of acini which appeared to have the form of a totally intact lobule it was simple to recognize other acini which, through excessive production of connective tissue, were separated into isolated groups. In those places in which destruction of the lobules reached enormous heights, there were many single acini scattered about, solid masses of epithelial cells and here and there only oval spaces in the connective tissue filled with colloid.

TABLE 6.—*Relative Frequency of the Changes in Connective Tissue and Parenchyma*

	Diffuse Struma (11 Cases)	Diffuse and Nodular Struma (16 Cases)	Nodular Struma (71 Cases)	Total (100 Cases)*
Increase in formation of connective tissue...	9 (81%)	11 (68%)	54 (76%)	74%
Edematous connective tissue.....	6 (54%)	1 (6.2%)	10 (14%)	17%
Papillae and cushion building.....	6 (54%)	.....	15 (27%)	21%
Desquamation of epithelial cells.....	6 (54%)	.....	16 (22%)	22%

\* This total includes two cases of atrophy of the thyroid gland.

Besides the degenerative changes in the parenchyma, it was possible to observe others of a regenerative nature. For example, one preparation showed a large space, bounded by cylindric epithelium, into which grew a large branched papilla. The central part of this space was filled with desquamated epithelium and occasional giant cells.

In not one of the histologic preparations did the degenerative changes lead to excessive sclerosis of the connective tissue or to a total destruction of the parenchyma such as one is likely to find in Riedel's struma. With this in mind, it would seem that the nonspecific chronic thyroiditis in the one hundred cases here discussed lies somewhere near the lower boundary of this form of thyroid disease.

# ROENTGEN IRRADIATION OF THE OVARIES AS SUPPLEMENT TO SURGICAL AND RADIUM THERAPY FOR MAMMARY CANCER

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The relationship between ovarian secretion and the growth and development of the breasts has been observed clinically for many years. With increasing knowledge of ovarian function, especially along hormonal lines, evidence is being accumulated to suggest the dependency of mammary activity on ovarian and anterior pituitary hormones. The former cause development of the breasts at puberty and their rhythmic changes associated with the menstrual cycle. The latter, when pregnancy intervenes with its preparation of the breasts for lactation, induce the secretion of milk. Because the ovarian hormones, especially the estrogenic principle, are growth-promoting factors in normal mammary development and because cancer is essentially an unrestricted growth, it is not illogical to deduce that in pathologic conditions of the breast, such as carcinoma, these hormones may stimulate malignant as well as mammary growth. The hypothesis advanced in this paper, therefore, is that in patients with cancer of the breast, whether it is primary or secondary, operable or inoperable, recurrent or metastatic, all ovarian secretion and activity should be destroyed by means of high voltage roentgen irradiation or by radium.

Clinical evidence supporting this hypothesis extends back for many years. Schinzinger,<sup>1</sup> in 1889, suggested bilateral oophorectomy in the treatment of carcinoma of the breast, and Beatson,<sup>2</sup> in 1896, reported three cases of mammary cancer in which therapeutic extirpation of the ovaries had been performed. For a short period oophorectomy enjoyed considerable vogue as an auxiliary treatment for inoperable cancer of the breast. Thomson,<sup>3</sup> in 1902, removed both ovaries from eighty patients with mammary carcinoma and noted a decided improvement

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From the Department of Gynecology, School of Medicine, Tulane University of Louisiana.

1. Schinzinger, cited by Taylor, G. W.: Artificial Menopause in Carcinoma of the Breast, *New England J. Med.* **211**:1138, 1934.

2. Beatson, G. T.: On the Treatment of Inoperable Cases of the Mammæ: Suggestions for a New Method of Treatment, with Illustrative Cases, *Lancet* **2**:109, 1896.

3. Thomson, A.: Analysis of Cases in Which Oophorectomy Was Performed for Inoperable Cancer of the Breast, *Brit. M. J.* **2**:1538 (Nov. 8) 1902.

in 22.5 per cent. Lett,<sup>4</sup> in 1905, reported ninety-nine cases in which oophorectomy had been performed, improvement being noted in 36 per cent. Subsequently, sporadic reports appeared describing oophorectomy as a supplementary therapy for malignant growths of the breasts, but because of the then attendant danger in removing both ovaries interest in this procedure gradually died.

It is interesting to observe that the majority of the early writers recorded improvement after oophorectomy in a fair percentage of cases of cancer of the breast. Regression of lesions lasting months or even years is described. In general, however, this method of supplementary therapy was applied by that group of workers only to inoperable or recurrent malignant growths of the breast.

With the advent of the roentgen rays, castration by irradiation was suggested as a substitute for Beatson's<sup>2</sup> operative procedure in the treatment of inoperable carcinoma of the breast, but it was not until many years later that this method of therapy was applied. Since 1920 Wintz<sup>5</sup> has used roentgen irradiation of the ovaries as a routine treatment in cases of cancer of the breast. In 1922 Ahlbom<sup>6</sup> began to use a similar method of treatment, reporting improvement in 73 per cent of the patients in a group over 45 years of age, as compared with the results in controls. Kaplan,<sup>7</sup> in 1927, recommended castration by irradiation in the treatment of inoperable cancer of the breast, and recently Hoffman<sup>8</sup> observed the disappearance of metastases to the scalp from carcinoma of the breast after roentgen irradiation of the ovaries. Daland<sup>9</sup> and Martin<sup>10</sup> also commented on the impressive and dramatic regressions of metastases from malignant tumors of the breast after roentgen irradiation of the ovaries.

There is also extensive laboratory evidence to support the hypothesis that an artificially induced menopause is an aid to surgical intervention

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4. Lett, H.: An Analysis of Ninety-Nine Cases of Inoperable Carcinoma of the Breast Treated by Oophorectomy, *Lancet* 1:227 (Jan. 28) 1905.

5. Wintz, H.: Experiences in the Irradiation of Breast Cancer, *Brit. J. Radiol.* 31:150, 1926.

6. Ahlbom, H.: Castration by Roentgen Rays as an Auxiliary Treatment in the Radiotherapy of Cancer Mammæ at Radiumhemmet, Stockholm, *Acta radiol.* 11:614, 1930.

7. Kaplan, I. I.: Twin Pregnancy After Temporary Suppression of Menstruation Following Roentgen-Ray Treatment for Mammary Cancer, *Am. J. Obst. & Gynec.* 14:40, 1927.

8. Hoffman, W. J.: Spontaneous Disappearance of Metastatic Nodules from Carcinoma of Breast Following Irradiation of Ovaries, *S. Clin. North America* 13:494, 1933.

9. Daland, E. M.: Cancer of the Breast, *Am. J. Cancer* 15:2361, 1931.

10. Martin, C. L.: New Developments in Irradiation Therapy of Breast Cancer, *Texas State J. Med.* 29:186, 1933.

and radium therapy in the treatment of mammary carcinoma. Interest in the relationship between the estrogenic hormone and the carcinogenic compounds has been intensified by the fact that certain substances which produce carcinoma in animals are somewhat similar chemically to the estrogenic substances and even produce estrous changes.<sup>11</sup> On the basis of an excellently presented comparison of the estrogenic hormones and the carcinogenic compounds Loeb<sup>12</sup> stated that one may conclude that: (1) there are substances which are both carcinogenic and estrogenic; (2) there are carcinogenic substances which are not estrogenic; (3) there are estrogenic substances which are not carcinogenic, and (4) even in cases in which the compounds are both estrogenic and carcinogenic, there is no parallelism between them in the strength of their activity.

The molecular structures of the estrogenic and carcinogenic compounds 1, 2-benzpyrene, 5, 6, cyclopenteno-1, 2-benzanthracene and 1, 2, 5, 6-di-benzanthracene, which are nonsaturated hydrocarbons possessing the tricycle phenanthrene ring, are similar. The actions of these principles are also somewhat similar, as each exhibits growth-promoting properties involving epithelial tissue primarily. Their action differs, however, in that the estrogenic hormone is essentially a sexual growth-stimulating factor affecting especially the female genital tract and mammary glands, while the action of the carcinogenic agent is stimulation of the growth of any and all body tissue.

Dodds,<sup>13</sup> in 1931, issued the following warning: "I do not think that the amazing potency of theelin (the estrogenic hormone) is recognized by the majority of cancer research workers. It is capable of producing the most extensive tissue proliferation and cell growth, and this appears to me to be of the utmost importance." Administration of an estrogenic substance results in hypertrophy and hyperplasia of all the female secondary sexual organs, including the breasts, while castration (lack of the estrogenic principle) in female mice under 6 months of age leads to marked retardation of the rate of growth and lowered incidence of spontaneous mammary cancer in susceptible strains.<sup>14</sup> Cas-

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11. Cook, J. W.; Dodd, E. C., and Hewett, C. L.: Synthetic Oestrous-Exciting Compound, *Nature*, London **131**:56, 1933.

12. Loeb, L.: Estrogenic Hormones and Carcinogenesis, *J. A. M. A.* **104**:1597 (May 4) 1935.

13. Dodds, E. C.: Recent Biological Research in Cancer, *Am. J. Cancer* **15**:2765, 1931.

14. Lathrop, A. S. C., and Loeb, L.: Rôle of Internal Secretion on the Spontaneous Development of Mouse Tumors, *J. Cancer Research* **1**:1, 1916. Loeb, L., and Genther, I. T.: Heredity and Internal Secretion on Origin of Mammary Cancer in Mice, *Proc. Soc. Exper. Biol. & Med.* **25**:809, 1928. Cori, C. F.: The Influence of Ovariectomy on the Spontaneous Occurrence of Mammary Carcinoma in Mice, *J. Exper. Med.* **45**:983, 1927.

tration does not prevent, however, the experimental production of mammary cancer by carcinogenic agents. The effect of castration is greater the earlier it is done. If castration is performed at a late age or after inoculation with tumor tissue, a less pronounced decrease in the incidence is noted, and retardation of growth is less effective.<sup>15</sup> Castration has no effect on the rate of growth of sarcoma<sup>16</sup> or cancer of the skin in animals.<sup>17</sup> This undoubtedly is due to the fact that the estrogenic principle is only a sexual growth-stimulating factor and not a general body-stimulating agent. The limitation of estrogenic activity to secondary sexual tissue—the breasts, uterus, vagina and tubes—explains the conflicting results reported concerning the action of the hormone in experimental work on cancer, a fact which is not generally recognized. This specific and limited character distinguishes the action of the estrogenic hormone from that of the carcinogenic factor. There is at present no evidence to prove that the carcinogenic compounds develop in the animal body from the estrogenic hormone.<sup>18</sup> Loeb,<sup>12</sup> however, demonstrated that spontaneous mammary carcinoma occurred earlier in a cancer-hereditary strain of mice which had been given the estrogenic hormone.

In addition to clinical and laboratory evidence, general observations support the hypothesis that roentgen irradiation of the ovaries, with subsequent estrogenic inactivity is beneficial as an auxiliary treatment to surgical intervention and radium therapy in the treatment of carcinoma of the breast. The belief that local etiologic factors, such as lactation and trauma, cause malignant mammary tumor appears to be of less significance than formerly, while the theory that general systemic influences, such as hormonal stimulation, are a causative factor is becoming more important. Trout<sup>19</sup> claimed that carcinoma develops in the remaining breast in a high percentage of cases if pregnancy (with increased estrogenic activity) occurs subsequent to removal of one breast for carcinoma. The extremely malignant character of cancer of the breast as a complication of pregnancy is widely recognized, and evidence is accumulating, based on general clinical impressions, that suggests that

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15. Pribram, E.: Study of Tumor Immunity: XIV. Relation Between Sex Glands and Tumor Growth in the White Mouse, *Ztschr. f. Krebsforsch.* **39**:399, 1933.

16. Molnar, K.: Effect of Estrogenic Agents on Transplanted Tumors, *Ztschr. f. Krebsforsch.* **38**:188, 1932.

17. Bischoff, F.; Maxwell, L. C., and Ullmann, H. J.: Hormones in Cancer: III. Effects of Glandular Extirpation, *J. Biol. Chem.* **80**:92, 1931.

18. Cook, J. W., and Dodds, E. C.: Sex Hormones and Cancer Producing Compounds, *Nature, London* **131**:205, 1933.

19. Trout, H. H.: The Remaining Breast After Radical Removal of the Opposite Side for Carcinoma, *Surg., Gynec. & Obst.* **34**:630, 1922.

carcinoma of the breast is many times more malignant and less curable in young women, in whom the estrogenic hormone is still active, than in patients who have passed the menopause.

As previously stated, the growth-promoting action of the estrogenic hormone is the main factor in mammary development at puberty. Watson reported marked development of the breasts in a girl 19 years of age with hypogonadism and amenorrhea, who was given the estrogenic hormone in large doses. Geschickter, Lewis and Hartman<sup>20</sup> investigated the action of this hormone on hypertrophy of the breast and the formation of a tumor. They concluded that gynecomastia in the male and virginal hypertrophy and fibro-adenoma in the female breast are dependent on pathologic variations in the action of the estrogenic hormone on the duct epithelium and surrounding breast tissues. These observers have demonstrated the presence of the estrogenic principle in a fibro-adenoma of the breast.

Since the rate of growth of mammary cancer in animals is accelerated by the estrogenic principle, and since hypertrophy of the breast and the formation of a benign tumor in human beings are also influenced by this hormone, it seems logical to conclude that a malignant growth of the human breast may likewise be affected by the action of the estrogenic hormone. This seems especially true in view of the fact that bilateral oophorectomy retards the rate of growth of a malignant tumor of the human breast and causes regression of metastatic nodules. In the treatment of mammary carcinoma, therefore, all estrogenic activity should be destroyed by roentgen irradiation of the ovaries, since the presence of the hormone is an exciting growth factor on the breast and on the mammary cancer. If the patient is still in her functional years, this type of therapy, in addition to surgical intervention, is all the more necessary, although Taylor<sup>21</sup> suggested that sometimes benefit may be derived from roentgen irradiation of the ovaries after the menopause. Induction of the menopause, especially in young women, in the treatment of carcinoma of the breast may seem somewhat radical, but in view of the tremendous growth-promoting properties of the estrogenic principle on secondary sexual tissue, this treatment is very rational. Its value might be demonstrated by an analysis of a series of five year cures of cancer of the breast before and after the menopause. If elimination of estrogenic activity is beneficial in the treatment of malignant mammary growth, there should be more cures of this condition in women who have passed the menopause, when the estrogenic hormone

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20. Geschickter, C. F.; Lewis, D., and Hartman, C. G.: Tumors of the Breast Related to the Oestrin Hormone, *Am. J. Cancer* **21**:828, 1934.

21. Taylor, G. W.: Artificial Menopause in Carcinoma of the Breast, *New England J. Med.* **211**:1138, 1934.

has ceased to function. The age element and the extent of the malignant growth should, of course, be taken into consideration.

#### CANCER OF THE FEMALE GENITAL ORGANS

Cancer of the female genital organs is included in this discussion only because the estrogenic hormone exerts the same growth-stimulating influence on these organs as it does on the mammary glands. If it is rational to destroy estrogenic activity in the treatment of mammary cancer, it is equally rational to eliminate the growth-promoting effect in cases of genital malignant growths. This is usually done. In the treatment of cancer of the cervix of the uterus a sufficient amount of radium is used to induce cessation of all ovarian and estrogenic activity. Also, in cases of a malignant growth of the fundus, the uterus, tubes and ovaries are generally removed and the estrogenic element thus destroyed. In cases of carcinoma of the ovaries the estrogenic hormone is probably ineffective as a growth stimulant, since it does not influence the organ directly. Surgical intervention and high voltage roentgen therapy, however, will usually remove all estrogenic effect. On the other hand, surgical treatment of cancer of the vulva or of the lower part of the vagina should be accompanied by inactivation of the estrogenic hormone, as in the case of malignant growths of the breast.

#### SUMMARY

A hypothesis is advanced that roentgen irradiation of the ovaries, with the elimination of the estrogenic activity, might be beneficial as a supplement to radical mastectomy and radium therapy in the treatment of malignant tumor of the breast. The earlier encouraging results obtained from bilateral oophorectomy and the laboratory evidence suggesting that the estrogenic hormone stimulates the growth of secondary sexual tissue and of tumor support this hypothesis. Only clinical application of this auxiliary therapy will prove its value.



# ACUTE CEREBRAL INJURIES

## ANALYSIS OF TEMPERATURE, PULSE AND RESPIRATION CURVES

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During the past decade, since the introduction of methods for cerebral dehydration, the treatment of acute cerebral injuries has become complicated. During this time there has been an increasing tendency in the diagnosis of such lesions for the physiologic reaction of the organism to intracerebral pressure to be superseded by mechanical measurement of intracerebral pressure. Treatment has been guided by the degree of spinal fluid pressure as recorded on the manometer without consideration of the natural defenses of the body or the manifestations that arise when these defenses have reached their limits. Cerebral tissue that is already traumatized has been further insulted by chemical solutions or by intermittent shifts in pressure produced by drainage of the spinal fluid. Finally, the current classifications of these injuries are open to the criticism that they cannot accurately convey the extent of intracerebral damage or aid in most instances in the treatment of the damage. In an effort to present a clinical and physiologic basis for the classification, diagnosis and therapy of acute cerebral injuries, 300 consecutive patients with such injuries admitted to the neurosurgical service of the Johns Hopkins Hospital have been studied.

The present classifications of cerebral injuries have been established on purely anatomic and pathologic foundations; they have been erected on what the eye can see and the hand can feel at operation or at autopsy. They have disregarded the reaction of the body to different grades of trauma. This manner of classifying cerebral injuries can be of no clinical assistance in evaluating the extent of intracerebral damage and the resulting pressure. It is possible, however, to formulate from a given series of cases a classification which will answer this purpose (table 1).

Trauma to the brain produces the same sequelae as trauma elsewhere in the body, namely, edema, hemorrhage and destruction of tissue of different degrees according to the type and extent of the exciting force. These sequelae, because the skull may be considered a closed box and inexpandible, produce the condition known as intracerebral pressure. By decreasing the vascular bed, tissue fluid and ventricular space, the

brain is able to compensate for a mild degree of pressure. If the pressure overcomes these natural defenses, death results unless surgical intervention is employed. Death results from anemia of the so-called vital centers in the medulla oblongata, that is, those centers regulating cardiac and pulmonary action and controlling the temperature. These nuclear aggregations are peculiarly sensitive to alterations in the cerebral pressure, and with the state of consciousness, their reactions may be recorded as curves for temperature and for pulse and respiratory rates and may be used as fundamental guides for the handling of the patient. On the basis of these guides, acute injuries to the brain may be divided into four groups, a classification that is both of diagnostic and of therapeutic aid.

TABLE 1.—*Anatomic and Pathologic Classification of Cerebral Injuries Based on Three Hundred Cases*

Anatomic consideration	No. of Cases
Fracture of the skull	
Vault.....	102
Base.....	122
Combined.....	56
Depressed.....	20
Total.....	300
Pathologic consideration	
Injury to the brain	
Cerebral concussion.....	213
Cerebral concussion with local cortical laceration.....	2
Local cortical laceration with acute subdural hematoma.....	5
Extradural hematoma.....	5
Cerebral edema.....	28
Cerebral edema with cortical laceration and petechial hemorrhage....	47
Total.....	300

#### CLASSIFICATION OF INJURIES TO THE BRAIN

*Type 1.*—Injury of this type occurred in the largest number of persons—213. One hundred and ninety of the patients were not operated on, and 23 underwent operation. On the whole, injury of this type represents that class of cerebral injury known as concussion, either with or without alteration in the structure of the skull. All the patients, however, did not show evidence of fracture of the skull. Injury of type 1 is characterized by an initial instantaneous loss of consciousness lasting but a few minutes, followed by a return to complete consciousness or a varying period of drowsiness. The temperature curve, after an early drop or after starting from a normal level, shows mild hyperpyrexia of perhaps 101 F. rectally and a slow, regular decline to normal within from twenty-four to seventy-two hours. The curve for the pulse rate closely follows the temperature curve, rising steadily with it after an initial irregularity and falling to normal in the same length of time. The respirations are normal, or during the period in which the

temperature rises, they may show a slight but regular retardation. In only 4 cases in this group were there significant changes in the respiratory action, whereas in all there were identical temperature and pulse curves. All the patients portrayed the state of consciousness mentioned previously. The patients operated on included those suffering from simple depressed fractures necessitating elevation of bone fragments without further relief from pressure. There were nine fatalities, due entirely to complications, such as pneumonia and meningitis, giving a

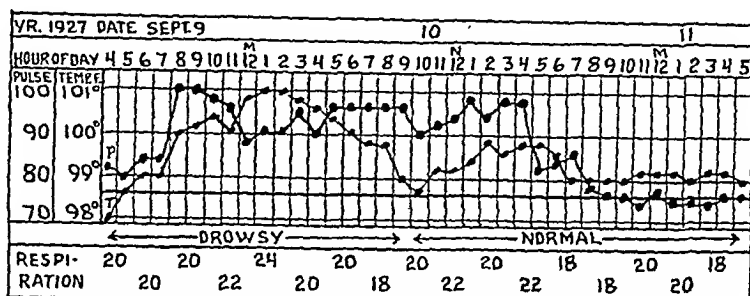


Chart 1.—Typical clinical record of an adult with cerebral injury of type 1.

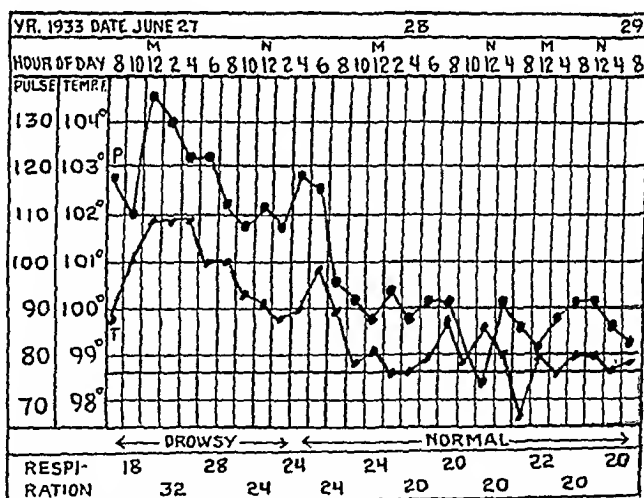


Chart 2.—Typical clinical record of a child with cerebral injury of type 1.

mortality of 2.06 per cent in the cases in which operation was not performed and 17.39 per cent in those in which operation was performed. Representative charts, as compiled at the bedside, are illustrated by charts 1 and 2, the first demonstrating the reaction to injury in an adult and the second the more active response in a child.

Injuries to the brain that fall into the next two groups by virtue of a state of consciousness and representative curves for the tempera-

ture and pulse and respiratory rates are the most interesting and the most amenable to surgical intervention when the natural defenses of the body collapse. It is obvious that the surgeon has no active part to play in cases of injury of type 1, except that of closely observing the patient and possibly of reconstructing a depressed skull. The compensatory mechanism of the brain is able to control the mild degree of pressure in this group. Unless complications arise, there will be no fatalities due to intracerebral pressure alone. The patient with an injury of this type will survive in spite of or regardless of specific methods of treatment directed toward relief from pressure. The next two types of injury were found in 36 and 24 cases, respectively, comprising 20 per cent of the total series.

*Type 2.*—Injury of this type occurred in 36 persons. It is chiefly characterized by the appearance of either early or late bradycardia, associated with a slight and persistent rise in temperature, rarely greater than 101 F. rectally, and by a respiratory rate which sometimes varies from the normal. In this group the respiratory rate was normal in all but 12 cases. The initial loss of consciousness may last but a few minutes but usually is prolonged. Throughout the course of the disability, the patient shows a more extensive loss of consciousness, varying from drowsiness to restlessness to periods of hyperactivity contrasting with semicoma. The state of consciousness may coincide with the gravity of the bradycardia. After a short initial rise, the slow, heavy, pounding pulse may develop early, or as pressure increases, from an extradural hematoma for instance, the retardation in the pulse rate may make its appearance late. The temperature, as noted, rarely exceeds 101 F. rectally and becomes normal when and if the bradycardia disappears. In 8 of the cases there was a slow, regular and deep respiratory excursion during the bradycardic interval; in 4 others there was an early, shallow irregularity in the respiratory rate. At no time did the latter present the clearcut curves portrayed by the temperature and pulse rate. This persistent, regular bradycardia may be considered evidence of compensated intracerebral pressure. The earliest irregularity in the bradycardia, the slightest rise in temperature or the briefest deepening in the state of consciousness are warning signals that the limits of compensation have been reached. It will be noted in the following charts that even simple bradycardia, without irregularity in temperature, respiratory rate or state of consciousness, is a potentially dangerous manifestation.

Chart 3 is the clinical record of a patient with early bradycardia, an elevated temperature and a normal respiratory rate. The state of consciousness was always good. This points to the fact that a certain degree of pressure may affect these various indexes differently. The

entire pattern of the injury must be evaluated as a whole. This chart demonstrates a condition of compensated intracerebral pressure.

Chart 4, made in a fatal case of cerebral injury, presents a clinical record that is typical for a patient with injury of type 2. The state of consciousness remained fairly adequate until a generalized convulsion ensued. There was slight if any change in the body temperature, and

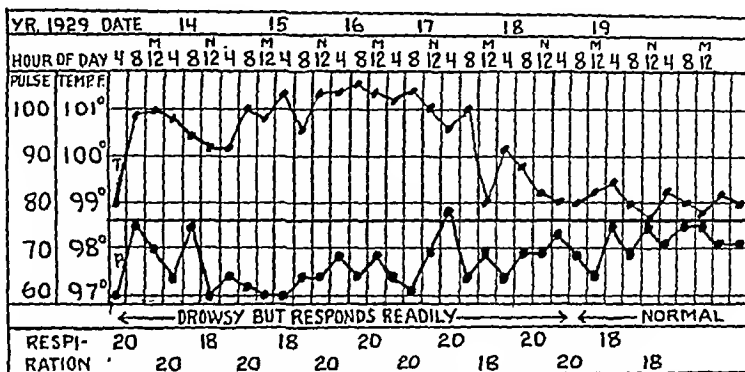


Chart 3.—Clinical record of a patient with cerebral injury of type 2.

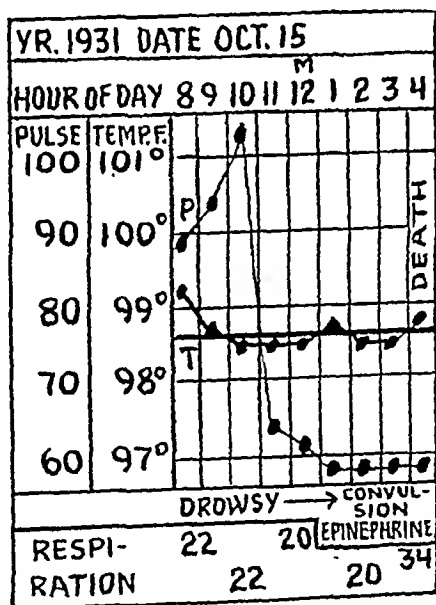


Chart 4.—Typical clinical record of a patient with a fatal cerebral injury of type 2.

the respiratory rate was normal until shortly before death. As may be seen, there was marked bradycardia. While the operating room was being prepared, the patient succumbed to pulmonary edema, following the injudicious use of epinephrine.

Chart 5 records the data in a similar case. Neither of these persons showed marked blunting of the state of consciousness. Both fell into coma without warning other than that furnished by the development of bradycardia.

Twenty-one persons in this group underwent an operative procedure, namely, subtemporal decompression. There were 4 fatalities, making a mortality of 17.39 per cent as compared to that of 25 per cent in the group of cases in which operation was not performed. The effects of the permanent relief from pressure obtained by subtemporal decompression are seen in charts 6, 7 and 8. The first two charts show an initial bradycardia and a rise in temperature with a rapid decline in the state of consciousness not compatible with further conservative treatment. Chart 6 shows that after operation the bradycardia returned,

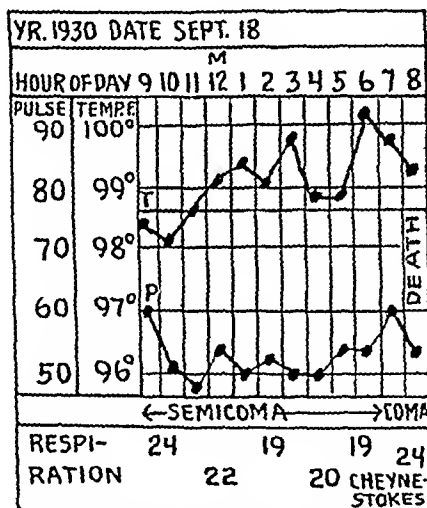


Chart 5.—Typical clinical record of a patient with a fatal cerebral injury of type 2.

with a rising state of consciousness, however, and a falling temperature curve. Chart 7 shows that after operation the clinical picture was similar to that produced by simple concussion or by a simple degree of pressure, as noted in the cases of injury of type 1. Chart 8 shows bradycardia developing over a period of three days and, after removal of an acute subdural hematoma for relief from pressure, reversion to the picture presented in cases of injury of type 1 after the pressure has been relieved.

Type 3.—Injury of this type occurred in 24 cases. It represents the second type of injury, for which surgical intervention is indicated and most often successful. In but few cases in this group were the



record of a patient with this degree of injury. Death occurred suddenly much the same as in the cases of injury of type 2, in which there was apparently compensation.

Chart 10 shows another example of a clinical record in a case of injury of this type. There was an initial rise in the temperature and

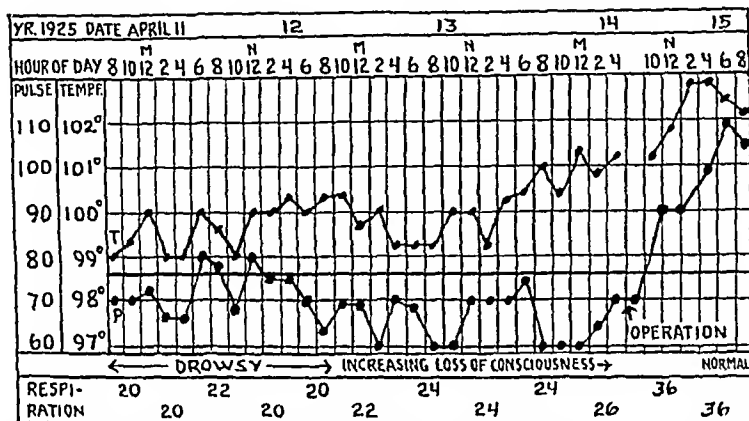


Chart 8.—Clinical record of a patient with cerebral injury of type 2 on whom subtemporal decompression was performed.

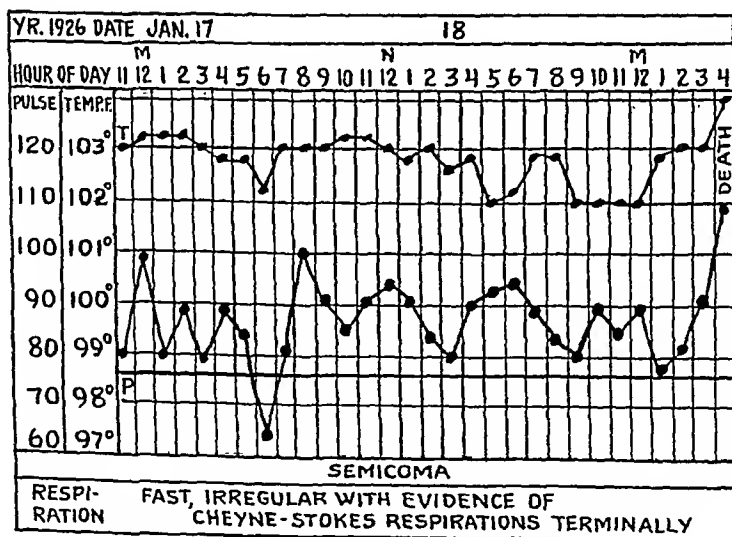


Chart 9.—Typical clinical record of a patient with cerebral injury of type 3.

the pulse rate, coma and a fairly normal respiratory rate, followed by a rise in the state of consciousness and then by a "break" in compensation and deepening coma. A subtemporal decompression afforded permanent relief from pressure, and the clinical record reverted to that representative of a type 1 injury.



Chart 11 shows the clinical record made in a case of similar injury, in which after early surgical intervention there was reversion to a clinical picture resembling that seen in cases of injury of type 2. In such a

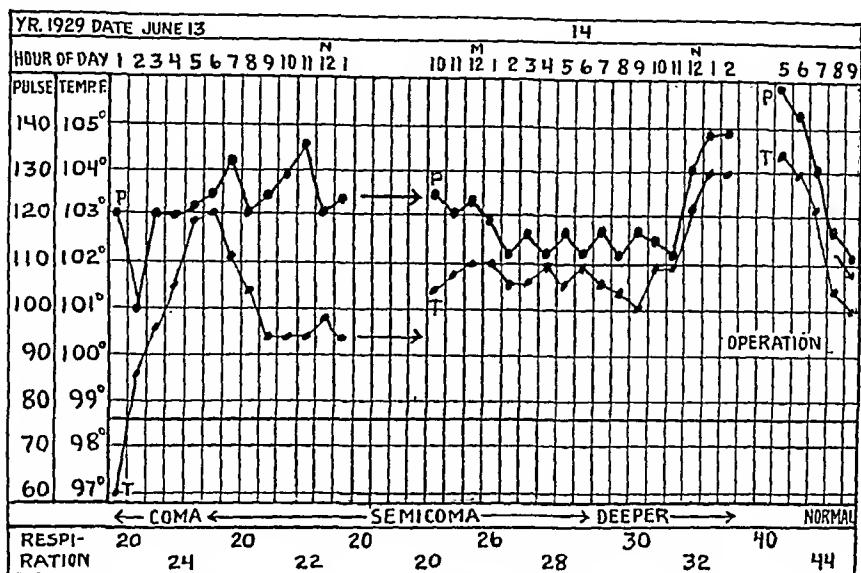


Chart 10.—Clinical record of a patient with cerebral injury of type 3 on whom subtemporal decompression was performed.

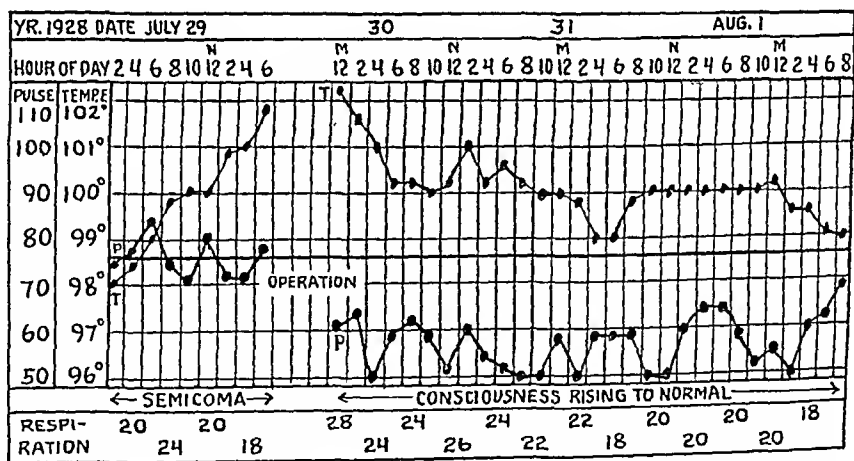


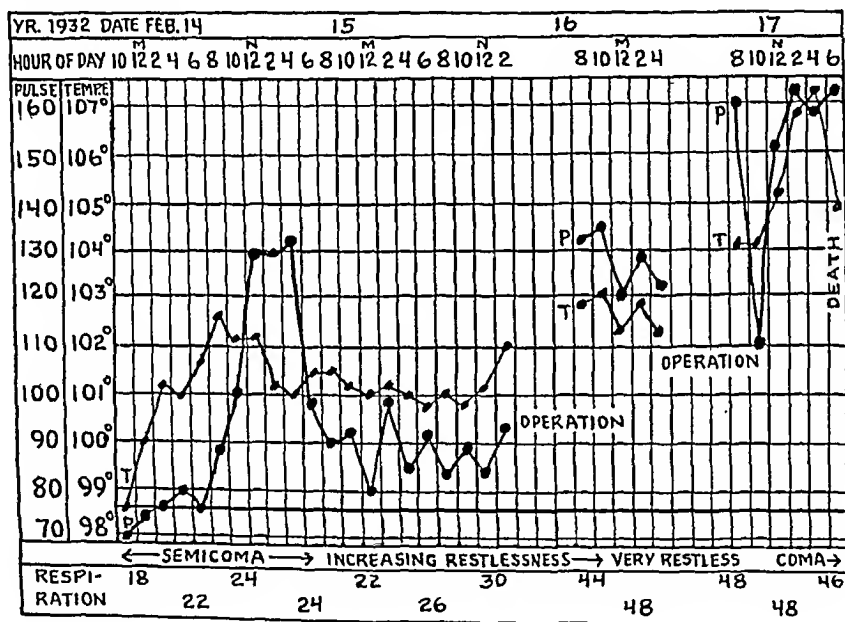
Chart 11.—Clinical record of a patient with a cerebral injury of type 3 on whom early surgical intervention was performed.

case the bradycardia may be watched less anxiously because permanent relief from pressure has been obtained.

Finally, chart 12 shows the clinical record made in a case of injury of type 3, in which bilateral decompression was unsuccessful in obtaining relief. The failure of the pressure curve to assume either one of

the less formidable outlines and the observation that the state of consciousness was not relieved following the first decompression made, were clinical guideposts that severe pressure was still present. In this case the cerebral damage was overwhelming.

*Type 4.*—Injury of this type includes trauma of such a severe degree that no procedure is successful in nullifying the effects of intracerebral pressure. It is clearly signalized by immediate and lasting coma, a rapidly rising pulse rate and temperature and a respiratory rate that approaches the Cheyne-Stokes type in coloration. Twenty-seven patients in the entire series had injuries of this type. Those on whom



the cases in which operation was not performed was 12.06 per cent, in the cases in which operation was performed, 45.55 per cent, and for the entire group, 18.66 per cent. It is evident from a consideration of the number of deaths and survivals in the cases of injury of all types in

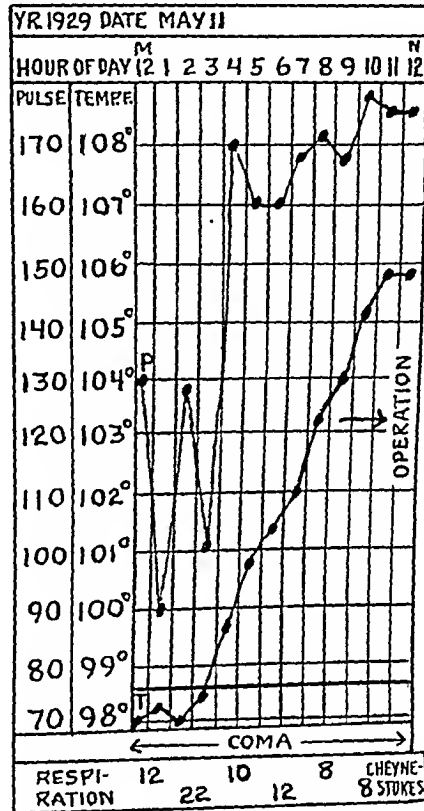


Chart 13.—Typical clinical record of a patient with cerebral injury of type 4.

TABLE 2.—Mortality Rates in Three Hundred Cases of Injury to the Brain

Type of Injury	No. of Patients Not Operated On		Percentage of Mortality	No. of Patients Operated On		Percentage of Mortality	Total
	Living	Dead		Living	Dead		
1.....	185	5	2.12	19	4	17.39	213
2.....	12	3	25.00	17	4	19.04	36
3.....	2	3	66.66	9	10	47.36	24
4.....	0	13	100.00	0	14	100.00	27
Total.....	199	24	10.76	45	32	41.55	300
Total percentage of mortality.....							18.66

which operation was performed and those in which it was not performed that the following statements may be made:

1. All patients with injury of type 1 and a certain diminishing percentage of those with injuries of types 2 and 3 will progress satisfac-

torily without operation; a small number will die because of complications.

2. A much larger number of patients with injuries of types 2 and 3 will demand operative intervention; if depressed fractures of type 1 are included, the percentage rises.

3. There is a definite percentage of patients who will die whether they are operated on or not.

If cases of depressed fractures in which there is no rise in intracerebral pressure are excluded, one may state that in 78 per cent of

TABLE 3.—*Causes of Injury and Results*

Results	Cause of Injury		
	Blow	Vehicle	Fall
Without operation			
Living.....	20	122	57
Dead.....	2	11	11
With operation			
Living.....	13	25	7
Dead.....	4	15	13
Total			
Living.....	33	147	64
Dead.....	6	26	24
Total.....	39	173	88
Percentage.....	13	58	29

TABLE 4.—*Röntgenographic Findings*

	Living		Dead		Total
	With Operation	Without Operation	With Operation	Without Operation	
Röntgenograms taken.....	16	137	4	3	160
Normal picture.....	5	38	1	1	45
Röntgenograms not taken.....	15	62	26	21	124
Injury visualized.....	14	8	2	1	25
Contrecoup.....	0	5	0	0	5

cases of acute injury to the head there is no necessity for active surgical intervention; in 13 per cent, surgical intervention is indicated and will be helpful, and in 9 per cent, the outcome is always fatal and no procedure will be effective.

Tables 3 to 11 are a part of this study, and the data presented in them are self explanatory.

After the degree of intracerebral pressure present in any patient has been ascertained by his physiologic reactions to that pressure, operative intervention is employed if compensation is at a dangerous level or if it has reached its limit. Table 12 shows the procedures performed on 77 patients and the outcome after each type of operation. It will be seen that unilateral or bilateral subtemporal decompression was the

TABLE 5.—*Local Injury to the Scalp*

Type of Injury	Living	Dead	Total
Laceration.....	77	20	97
Hematoma or edema.....	74	23	97
Contusion.....	68	6	74
None noted.....	25	7	32
Position of Injury			
Left side of cranium.....			108
Right side of cranium.....			121
Bilateral.....			39

TABLE 6.—*Drainage of Hemorrhagic Fluid or Spinal Fluid from Cranial Orifices\**

Position of Drainage	Living	Dead	
Ear alone.....	56	8	
Both ears.....	1	0	
Nose.....	33	11	
Mouth.....	8	1	
Combination.....	22	14	Total 154
No bleeding.....	124	22	Total 146
Total.....	244	56	

\* In about one half of the cases there was drainage of hemorrhagic fluid or of spinal fluid from the cranial orifice. Drainage from the ear is of little significance, whereas drainage from the nose or from a combination of orifices is potentially more dangerous. Of the patients with evidence of drainage, 21.9 per cent died; of those without such evidence 15.1 per cent died.

TABLE 7.—Data on Respiratory Rate

[illegible]

TABLE 8.—*Neurologic Signs and Symptoms*

General Signs	Living	Dead	Total	Localizing Signs	Living	Dead	Total
Drowsiness.....	132	7	139	Localized convulsion.....	12	6	18
Semicomatous.....	21	5	26	Hemiplegia.....	26	11	37
Coma.....	0	15	15	Hyperreflexia, local.....	5	4	9
Late coma.....	13	2	15	Spasticity, local.....	1	1	2
Coma versus hyperactivity..	11	6	17	Areflexia, local.....	0	1	1
Restlessness.....	15	4	19	Babinski sign, unilateral....	7	10	17
Irrational.....	13	2	15	Ankle clonus, unilateral....	1	4	5
Vomiting.....	109	11	120	Aphasia.....	4	1	5
Headache.....	50	1	51	Involvement of sixth nerve..	3	2	5
Involuntary voiding.....	2	1	3	Involvement of fifth nerve,			
Generalized convulsion.....	7	6	13	sensory.....	2	0	2
Generalized hyperreflexia....	3	4	7	Involvement of eighth nerve	9	0	9
Babinski sign, bilateral.....	9	1	10	Involvement of seventh			
Kernig sign, bilateral.....	0	1	1	nerve.....	8	0	8
Ankle clonus, bilateral.....	3	3	6	Tinnitus.....	1	0	1
Areflexia, bilateral.....	1	11	12	Headache, localized.....	1	0	1
Cervical rigidity.....	3	3	6	Conjugate deviation of eyes:			
Amnesia.....	3	0	3	Toward lesion.....	6	2	8
Spasticity, generalized.....	0	1	1	Away from lesion.....	2	5	7
Small fixed pupils.....	3	4	7	Anisocoria:			
Dilated sluggish pupils.....	7	3	10	Pupil dilated on side of			
Dilated fixed pupils.....	2	1	3	lesion.....	11	3	14
Sluggish pupils.....	0	2	2	Pupil constricted on side			
Fixed pupils.....	0	1	1	of lesion.....	3	0	3
Rotatory nystagmus.....	3	0	3	Ptosis.....	1	0	1
Divergent squint.....	1	0	1	Involvement of third nerve..	2	0	2
Diplopia.....	2	0	2	Involvement of second			
Papilledema.....	0	1	0	nerve.....	2	1	3
Convergent squint.....	1	0	1				

TABLE 9.—*Data on Complications*

Type of Complication	Living	Dead	Type of Complication	Living	Dead
Alcoholism.....	32	9	Otitis media.....	1	0
Syphilis.....	6	1	Anuria.....	0	1
Peripheral fracture.....	14	6	Uremia.....	1	0
Axial fracture.....	12	6	Complications of V.....	1	0
Pneumonia.....	1	8	".....	0	1
Meningitis.....	2	5	".....	0	1
Scalp infection.....	1	0	Abdominal hemorrhage....	0	3
Peripheral abscess.....	1	0	Epinephrine (?).....	0	1
Traumatic psychosis.....	4	0	Burns.....	1	0
Myocardial failure.....	1	1	Hemothorax.....	0	1
Peripheral laceration.....	3	1	Pulmonary edema.....	0	2
Intra-orbital hemorrhage....	1	0	Rupture of eyeball.....	1	0
Acute gonorrhea.....	1	0	Exophthalmos.....	1	0
Résumé					
Complications			Living	Dead	Total
Without operation.....	58	14			72
With operation.....	13	20			33
No complications					105
Without.....	140	11			151
With.....	32	12			44
					195

TABLE 10.—*Causes of Death in Fatal Cases \**

Cause	Type 1 Injury	Type 2 Injury	Type 3 Injury	Type 4 Injury
Trauma.....	0	1	5	23
Meningitis.....	4	0	1	1
Pneumonia.....	2	2	5	0
Pulmonary edema.....	0	0	1	0
Epinephrine (?).....	0	1	0	0
Cardiac failure.....	1	0	0	0
Anuria.....	1	0	0	0
Preparation for operation:				
Pressure.....	0	2	1	1
Apoplexy.....	1	0	0	0

\* Overwhelming trauma plays the greatest rôle. Meningitis and pneumonia are the common fatal complications.

operation of choice when permanent relief from pressure was sought.

The results of a comparison of the four types of injury and the findings at operation are interesting and support the integrity of this method of classification. In cases of injury of type 1, there is little if any disturbance visible in the cerebral tissue itself. There is never diffuse edema. In 2 cases bloody fluid under tension was encountered, with occasional discoloration of the pia mater. Operation in cases of injury of types 2 and 3 revealed various grades of cerebral damage, all promoting a rise in pressure. Included in this group are cases of extradural hematoma in which the growth promotes symptoms of pressure

TABLE 11.—*Sequelae Noted at Discharge\**

Paralysis of eighth nerve, complete or partial.....	23
Paralysis of seventh nerve, partial.....	1
Paralysis of sixth nerve.....	1
Paralysis of third nerve.....	1
Paralysis of second nerve.....	2
Hemiplegia, spastic.....	1
Traumatic psychosis.....	4
To return for elevation of fragments.....	2

\* Thirty-five of 244 persons showed some type of residuum at the time of discharge from the hospital.

TABLE 12.—*Results of Operations*

Type of Operation	Type 1 Injury		Type 2 Injury		Type 3 Injury		Type 4 Injury		Total	Mortality, Per- centage
	Living	Dead	Living	Dead	Living	Dead	Living	Dead		
Elevation of fragments	18	..	2*	..	..	..	..	..	20	0
Unilateral subtemporal decompression.....	..	1	16	4	5	6	..	11	43	62
Bilateral subtemporal decompression.....	..	1	1	..	4	4	..	1	11	54
Trephination.....	..	..	..	..	..	2*	..	2	4	100
Osteoplastic bone flap..	..	..	..	..	..	1*	..	..	1	100
Cisternal drainage.....	1	2	..	..	..	..	..	..	3	66
Mortality, percentage..	17		19		52		100			

\* In conjunction with decompression.

by external compression. Also included in injuries of these types are vascular injuries to the cortex that give rise to subdural hematoma, moderate to severe cerebral edema and edema in some degree plus cortical laceration and some petechial hemorrhages. Operation in cases of injury of type 4 invariably revealed massive edema associated with cerebral laceration and multiple petechial hemorrhages. Autopsy was performed in 33 per cent of the cases.

#### THERAPY

The armamentarium necessary for the clinical study of acute cerebral injuries as outlined here is extremely simple. The service of a trained

TABLE 13.—Data on Operative Findings

Operative Picture	Type 1 Injury		Type 2 Injury		Type 3 Injury		Type 4 Injury		Total
	Living	Dead	Living	Dead	Living	Dead	Living	Dead	
Depression of skull; dura intact.	11	..	..	..	..	..	..	..	11
Depression of skull; dura torn...	3	..	..	..	..	..	..	..	3
Depression of skull; local corti-	4	..	..	..	..	..	..	..	4
" " " " " "	1	2	..	..	..	..	..	..	3
" " " " " " discolored; old bloody fluid....	..	2	..	..	..	..	..	..	2
Slight edema; brain otherwise normal; fluid under pressure...	..	..	..	..	1	..	..	..	1
Extradural hemorrhage.....	..	..	5	..	..	..	..	..	5
Subdural hemorrhage; cortical laceration.....	..	..	3	1	1	1	..	..	6
Moderate cerebral edema; fluid under pressure; occasional petechial hemorrhage.....	..	..	6	..	2	3	..	..	11
Severe cerebral edemas; occasional petechial hemorrhage	..	..	3	1	3	1	..	4	12
Massive cerebral edema; laceration of cortex; petechial hemorrhages.....	..	..	..	1	2	2	..	7	12
Combination of last four groups	..	..	..	1	..	3	..	3	7

## SUMMARY

Various supplementary tables are appended.



# LETHAL FACTORS IN BILE PERITONITIS

## I. "SURGICAL SHOCK"

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The mechanism of death in bile peritonitis has puzzled investigators for a number of years. Although the condition is rare clinically, its theoretical implications warrant a thorough consideration. In the present paper certain findings are reported that indicate that one of the lethal factors in bile peritonitis is a disturbance of fluid balance in the body resembling the so-called condition of surgical shock.

### RÉSUMÉ OF LITERATURE ON SURGICAL SHOCK

*Various Theories of Secondary Shock.*—During the first three decades of the present century the question of the mechanisms active in the production of surgical or traumatic shock centered chiefly around the theories of nervous<sup>1</sup> and of toxic origin. In Cannon's book<sup>2</sup> on the subject, published in 1923, he concluded: "The theory of secondary shock which has the strongest support both in clinical observations and in laboratory experiments is that of a toxic factor operating to cause an increased permeability of the capillary wall and a consequent reduction of blood volume by escape of plasma into the tissue." It was not until the past eight years that the work of Phemister and Handy,<sup>3</sup> Phemister,<sup>4</sup> Blalock<sup>5</sup> and Parsons and Phemister<sup>6</sup> indicated that in

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From the Douglas Smith Foundation and the service of Dr. Edmund Andrews, Department of Surgery, the University of Chicago.

1. Crile, G. W.: *An Experimental Research into Surgical Shock*, Philadelphia, J. B. Lippincott Company, 1899.

2. Cannon, W. B.: *Traumatic Shock*, New York, D. Appleton & Company, 1923.

3. Phemister, D. B., and Handy, J.: *Vascular Properties of Traumatized and Laked Bloods*, *J. Physiol.* **64**:155-173 (Nov. 21) 1927.

4. Phemister, D. B.: *The Vascular Properties of Traumatized and Laked Bloods and of Blood from Traumatized Limbs*, *Ann. Surg.* **87**:806-810 (June) 1928.

5. Blalock, Alfred: *Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury*, *Arch. Surg.* **20**:959-996 (June) 1930.

6. Parsons, Eloise, and Phemister, D. B.: *Haemorrhage and "Shock" in Traumatized Limbs*, *Surg., Gynec. & Obst.* **51**:196-207 (Aug.) 1930.

many instances of experimental traumatic shock a local escape of blood or blood plasma into the injured tissues is sufficient to account for any changes in blood pressure or blood volume that occur.

*Loss of Plasma-Like Fluid in Various Types of Experimental Secondary Shock.*—Some observers noted that in conditions aside from shock due to trauma to an extremity there was a localized loss of fluid into the injured tissues with a resultant fall in blood pressure and signs and symptoms of shock. In some instances this fluid was essentially similar to blood plasma. Blalock,<sup>7</sup> Underhill<sup>8</sup> and later Harkins<sup>9</sup> studied the importance of the local loss of fluid in the production of the low blood pressure after experimental burns. Harkins, Harmon and Hudson<sup>10</sup> showed that in experimental freezing there is a somewhat similar localized loss of plasma-like fluid, with a resultant blood concentration and low blood pressure. Johnson and Blalock<sup>11</sup> showed that intestinal manipulation in dogs produces an extensive weeping of the visceral peritoneal surfaces that is an important causative factor in the resultant shocklike syndrome. It is of interest to note that the results of Swingle and Parkins<sup>12</sup> are not entirely in agreement with

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7. Blalock, Alfred: Experimental Shock: VIII. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns, *Arch. Surg.* **22**:610-616 (April) 1931.

8. Underhill, Frank P.; Kapsinow, Robert, and Fisk, Merl E.: Studies on the Mechanism of Water Exchange in the Animal Organism: I. The Nature and Effects of Superficial Burns, *Am. J. Physiol.* **95**:302-314 (Nov.) 1930; II. Changes in Capillary Permeability Induced by a Superficial Burn, *ibid.* **95**:315-324, 1930; III. The Extent of Edema Fluid Formation Induced by a Superficial Burn, *ibid.* **95**:325-329, 1930; IV. The Composition of Edema Fluid Resulting from a Superficial Burn, *ibid.* **95**:330-333, 1930; V. The Relationship of the Blood Chlorides to the Chlorides of Edema Fluid Produced by a Superficial Burn, *ibid.* **95**:334-338, 1930; VI. The Composition of Tissues Under the Influence of a Superficial Burn, *ibid.* **95**:339-347, 1930.

9. Harkins, Henry N.: Shift of Body Fluids in Severe Burns, *Proc. Soc. Exper. Biol. & Med.* **31**:994-995 (May) 1934; Experimental Burns: I. The Rate of Fluid Shift and Its Relation to the Onset of Shock in Severe Burns, *Arch. Surg.* **31**:71-85 (July) 1935.

10. Harkins, H. N.: Shock Due to Freezing: I. Shift of Body Fluids and Associated Blood Concentration Changes, *Proc. Soc. Exper. Biol. & Med.* **32**:432-434, 1934. Harkins, H. N., and Hudson, J. E.: Shock Due to Freezing: II. Composition of Edema Fluid, *ibid.* **32**:434-435, 1934. Harkins, H. N., and Harmon, P. H.: Experimental Freezing: Bleeding Volume, General and Local Temperature Changes, *ibid.* **32**:1142-1143, 1935.

11. Johnson, G. S., and Blalock, Alfred: Experimental Shock: XII. A Study of the Effects of Hemorrhage, of Trauma to Muscles, of Trauma to the Intestine and of Histamine on the Cardiac Output and on Blood Pressure of Dogs, *Arch. Surg.* **23**:855-863 (Nov.) 1931.

12. Swingle, W. W., and Parkins, W. M.: A Comparative Study of the Effect of Trauma on Healthy Vigorous Dogs With and Without Adrenal Glands, *Am. J. Physiol.* **111**:426-439 (March) 1935.

those of Johnson and Blalock. Swingle and Parkins found that even two and one-half hours of vigorous intestinal stripping had little effect on the blood pressure.

*Loss of Blood in Various Types of Secondary Shock.*—In other instances of a shocklike syndrome, an extensive loss of almost pure blood into the injured tissues results. The effect of trauma to an extremity in dogs was further studied by Robinson and Parsons<sup>13</sup> and by Roome, Keith and Phemister.<sup>14</sup> Scott and Wangenstein<sup>15</sup> showed that the loss of blood in experimental intestinal strangulation had a close relationship to the degree of shock and to death. This loss occurred into the intestinal walls and lumens and was associated with a weeping of plasma-like fluid into the peritoneal cavity. It was much more extensive when the veins alone to the loop were ligated and less so when the arteries alone or the arteries and veins together were ligated. This is similar to the findings of Brooks<sup>16</sup> in Volkmann's ischemic palsy produced experimentally. Brooks found that this condition could be best simulated by ligation or obstruction of the veins alone to an extremity. In both the experimental and the clinical examples of Volkmann's palsy there is effusion of blood into the tissues with resultant swelling, although in general this swelling is not extensive enough to produce a shocklike syndrome. Elman and Cole<sup>17</sup> recently showed quantitatively that the rapid death which occurs after acute portal obstruction "is to be explained on the basis of a loss of blood from the systemic into the portal system of a sufficient magnitude to reduce blood pressure below that compatible with life." Domenech-Alsina, Benaiges and Arqué<sup>18</sup> showed that irrigation of the peritoneal cavity

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13. Robinson, Will, and Parsons, Eloise: Hemorrhage and "Shock" in Traumatized Limbs, *Arch. Path.* **12**:869-888 (Dec.) 1931.

14. Roome, N. W.; Keith, W. S., and Phemister, D. B.: Experimental Shock: The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods, *Surg., Gynec. & Obst.* **56**:161-168 (Feb.) 1933.

15. Scott, H. G., and Wangenstein, O. H.: Blood Pressure Changes Correlated with Time, Length and Type of Intestinal Strangulation in Dogs, *Proc. Soc. Exper. Biol. & Med.* **29**:428-431 (Jan.) 1932; Blood Losses in Experimental Intestinal Strangulations and Their Relationship to Degree of Shock and Death, *ibid.* **29**:748-751 (March) 1932.

16. Brooks, Barney: Pathologic Changes in Muscle as a Result of Disturbances of Circulation: An Experimental Study of Volkmann's Ischemic Paralysis, *Arch. Surg.* **5**:188-216 (July) 1922.

17. Elman, Robert, and Cole, Warren H.: Hemorrhage and Shock as Causes of Death Following Acute Portal Obstruction, *Arch. Surg.* **28**:1166-1175 (June) 1934.

18. Domenech-Alsina, F.; Benaiges, B., and Arqué, P.: Etude du choc provoqué par l'irrigation péritonéale hypertonique, *Compt. rend. Soc. de biol.* **114**: 104-105 (Feb. 12) 1933.

of dogs with a hypertonic solution (4 per cent) of sodium chloride gave rise to a progressive fall in blood pressure, a rise in the percentage of hemoglobin, a drop in the carbon dioxide reserve content of the blood and an increase in the blood chloride content. In some of the animals there was a sudden drop in the blood pressure just before death, as has been observed in secondary shock due to other causes.

*The Irreversibility of the Shock Syndrome.*—The physical explanation of various types of shock should not be accepted as the complete answer to the problem without careful consideration. It has long been known both clinically and experimentally that even the simplest of shocklike syndromes, namely, that following hemorrhage, is not always curable by restoration of the amount of blood that is lost. Blalock<sup>19</sup> has mentioned this fact, and it has previously been noted by others. As early as 1914 Pilcher and Sollmann<sup>20</sup> noted that after dogs were bled extensively, the blood pressure "can only be brought back to 60 mm. no matter how much fluid is injected." Schlossberg and Sawyer<sup>21</sup> showed in studies on hemorrhage in cats that if the blood pressure were "allowed to remain long at the shock level after the hemorrhage, it could not be permanently restored." The recent work of O'Shaughnessy and Slome<sup>22</sup> demonstrates that the local loss of fluid may not be the sole factor in the production of traumatic shock. From experiments on the degree of trauma necessary to produce shock in the presence of varying extents of reflex connections, they concluded that both local loss of fluid and discharge of nociceptive nervous stimuli are the effective etiologic agents. They stated: "The evidence does not allow us to dogmatize as to the relative importance of these factors, although we are inclined to believe that the nervous factor dominates the picture." Freeman,<sup>23</sup> Schlossberg and Sawyer<sup>21</sup> and others showed that the sympathetic nervous system has a direct controlling influence on the circulating blood volume and is to be reckoned with as a factor in the production of shock. Freeman also showed that hemorrhage gives

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19. Blalock, A.: Acute Circulatory Failure as Exemplified by Shock and Haemorrhage, *Surg., Gynec. & Obst.* **58**:551-566 (March) 1934.

20. Pilcher, J. D., and Sollmann, T.: Studies on the Vasomotor Center: The Effects of Intravenous Infusion of Normal Saline Solution, *Am. J. Physiol.* **35**: 70-72 (Aug.) 1914.

21. Schlossberg, T., and Sawyer, M. E. Mackay: Studies of Homeostasis in Normal, Sympathectomized and Ergotomized Animals: IV. The Effect of Hemorrhage, *Am. J. Physiol.* **104**:195-203 (April) 1933.

22. O'Shaughnessy, L., and Slome, D.: Etiology of Traumatic Shock, *Brit. J. Surg.* **22**:589-618 (Jan.) 1935.

23. Freeman, Norman E.: Hemorrhage in Relation to Shock: Experimental Effect of Intravenous Injections of Saline, Gum Acacia, and Blood on the Rate of Adrenal Secretion Resulting from Hemorrhage, *Ann. Surg.* **101**:484-493 (Jan.) 1935.

rise to a fall in blood pressure and to an increase in the secretion of epinephrine. This secretion produces stasis, leading to further loss of blood, and thus a vicious circle is established. Swingle and his co-workers<sup>24</sup> reported that bilateral adrenalectomy produces a syndrome that is similar to traumatic shock in thirty-one particulars. Later Swingle and Parkins<sup>12</sup> showed that dogs without adrenal glands were much more susceptible to trauma than normal dogs. Furthermore, when a shocklike condition was produced in adrenalectomized dogs, recovery followed the administration of extract of the adrenal cortex. Heuer and Andrus<sup>25</sup> showed that the shocklike syndrome produced after the intravenous injection of the contents of obstructed intestinal loops was ameliorated by injections of extract of the adrenal cortex.

It seems, therefore, that while the physical explanation of shock on the basis of local loss of fluid into the injured tissues is undoubtedly of importance, nervous factors may make the injured animal or patient more susceptible to this loss of fluid. Furthermore, overaction of the sympathetico-adrenal system or an insufficient supply of adrenal cortex hormone may result in a generalized leakage into the tissues of fluid from the blood in addition to the localized loss at the site of injury, producing a vicious circle. It has been shown by Brooks and Blalock<sup>26</sup> that when there is reduction of the blood volume even by simple hemorrhage there may be hemorrhagic involvement of the adrenal glands. This damage may in turn produce a secondary insufficiency of adrenal cortex hormone. The local loss of fluid into the injured tissue is undoubtedly of importance in the production of shock, but it does not entirely explain why the shock syndrome is so often irreversible. A too prolonged period of low blood pressure with damage to the tissue is frequently a factor in this irreversibility.

#### RÉSUMÉ OF LITERATURE ON BILE PERITONITIS

*Bile Peritonitis Without Demonstrable Perforation of the Gallbladder.*—The literature indicates a possible difference between human and experimental bile peritonitis. Mentzer<sup>27</sup> has collected reports of numerous cases of bile peritonitis in which the patient recovered, but he also found many reports which contained evidence of the toxicity

24. Swingle, W. W.; Pfaffner, J. J.; Vars, H. M.; Bott, P. A., and Parkins, W. M.: The Function of the Adrenal Cortical Hormone and the Cause of Death from Adrenal Insufficiency, *Science* **77**:58-64 (Jan. 13) 1933.

25. Heuer, G. J., and Andrus, W. DeW.: The Effect of Adrenal Cortical Extract in Controlling Shock Following the Injection of Aqueous Extracts of Closed Intestinal Loops, *Ann. Surg.* **100**:734-749 (Oct.) 1934.

26. Brooks, B., and Blalock, A.: Shock with Particular Reference to That Due to Hemorrhage and Trauma to Muscles, *Ann. Surg.* **100**:728-733 (Oct.) 1934.

27. Mentzer, S. H.: Bile Peritonitis, *Arch. Surg.* **29**:227-241 (Aug.) 1934.

of bile. To explain this, he mentioned the work of Brand,<sup>28</sup> who "showed that dog's bile contains eight times as much taurocholic acid as glycocholic acid, while human bile contains only from one-fifth to one-eighth as much" and who furthermore stated that taurocholic acid is from twelve to twenty times as toxic as glycocholic acid. However, Horrall and Carlson<sup>29</sup> noted no special difference in the toxicity of sodium taurocholate and sodium glycocholate and found that the cholate radical is the toxic component of the two. It is quite possible that in many instances the difference is to be explained by the fact that bile from the gallbladder has been used in most experimental studies, whereas in cases of bile peritonitis in human beings the leakage of bile is often from the common duct or liver, or from a gallbladder that has lost its concentrating power. In experimental studies in which bile from the common duct or a combination of bile from the common duct and from the gallbladder has been used, such as those of Ziegler and Orr,<sup>30</sup> the results have been inconstant and fatal results have been less frequent than when bile from the gallbladder alone was used. The recent work of Blalock<sup>31</sup> on experimental bile peritonitis produced by bile from the common duct obtained by means of a cannula also gave inconstant results. Blalock found that when 11 cc. of bile per kilogram of body weight, obtained by means of a cannula that had been in the common duct for one day, was injected intraperitoneally into another dog, death resulted. However, with 20 cc. of bile per kilogram of body weight, collected by means of a cannula that had been in the common duct for six days, death did not result. For the particular purpose in mind, Blalock's method was feasible, as he was attempting to study perforated peptic ulcer, and bile from the common duct is the type, if any, that would enter the peritoneal cavity in this condition.

The interesting condition of biliary peritonitis without apparent perforation of the bile tracts has often been reported in human beings. Clairmont and von Haberer<sup>32</sup> described bile peritonitis without demonstrable perforation in 1911. Later they postulated<sup>33</sup> that there must be

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28. Brand, J., cited by Mentzer.<sup>27</sup>

29. Horrall, O. H., and Carlson, A. J.: The Toxic Factor in Bile, *Am. J. Physiol.* **85**:591 (July) 1928.

30. Ziegler, A. M., and Orr, Thomas G.: Chemical Changes in the Blood of the Dog in Experimental Bile Peritonitis, *J. Exper. Med.* **53**:865-868 (June) 1931.

31. Blalock, Alfred: Experimental Studies on the Effects of the Perforation of Peptic Ulcers, *Surg., Gynec. & Obst.* **61**:20-26 (July) 1935.

32. Clairmont, P., and von Haberer, H.: Gallige Peritonitis ohne Perforation der Gallenwege, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **22**:154-158, 1911.

33. Clairmont, P., and von Haberer, H.: Gibt es eine gallige Peritonitis ohne Perforation der Gallenwege? *Wien. klin. Wchnschr.* **26**:891-892 (May 29) 1913.

a pathologic condition of the walls of the gallbladder or bile channels to permit this abnormal permeability. Sick and Fränkel<sup>34</sup> collected reports of eighteen cases of this interesting condition from the literature two years later. Cases have been reported by Sabadini and Curtillet,<sup>35</sup> Tormey,<sup>36</sup> Bundschuh,<sup>37</sup> Melchior,<sup>38</sup> Schievelbein,<sup>39</sup> and others. In the excellent bibliography on bile peritonitis in Wangensteen's<sup>40</sup> paper on the subject, reports of numerous instances without obvious perforation are collected. Nauwerck and Lübke<sup>41</sup> claimed that macroscopic examination alone is not sufficient to rule out the presence of a small tear or pinpoint opening in the biliary system. Blad<sup>42</sup> showed that in vitro the pigments in colloidal bile cannot pass through a membrane but that when a tryptic enzyme is added the colloids are destroyed and the pigment is "liberated," which then passes through the membrane. These results held true when a freshly removed gallbladder was used as a membrane. Blad elaborated these results in vivo in dogs by ligating the common duct and injecting nonsterile duodenal juice into the gallbladders of dogs. In these experiments the gallbladder became completely necrotic, and actual bile peritonitis without perforation resulted. The action was attributed to the tryptic enzymes in the duodenal juice. Risel<sup>43</sup> reported a case of sterile gangrene of the gallbladder in a human being, although in this instance he thought that the gangrene may have been due to a thrombotic process in the cystic artery rather than to a tryptic enzyme. Many cases in human beings may be cited to contradict the statement that necrosis of the wall of the gallbladder alone will lead to the escape of bile. These include instances of suppurative chole-

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34. Sick, C., and Fränkel, E.: Ein Beitrag zur sog. galligen Peritonitis, Beitr. z. klin. Chir. **85**:687-695 (July) 1913.

35. Sabadini, I., and Curtillet, E.: Les épanchements biliares intrapéritonéaux sans perforation apparente des voies biliares, J. de chir. **45**:191-232 (Feb.) 1935.

36. Tormey, Albert R.: Biliary Peritonitis Without Apparent Perforation, Wisconsin M. J. **33**:839 (Nov.) 1934.

37. Bundschuh, Eduard: Zur perforationslosen Gallenperitonitis, Arch. f. klin. Chir. **161**:549-557, 1930.

38. Melchior, Eduard: Zur Kenntnis der perforationslosen Gallenperitonitis, Deutsche Ztschr. f. Chir. **243**:458-463 (June 30) 1934.

39. Schievelbein: Ueber gallige Peritonitis ohne Perforation der Gallenwege, Beitr. z. klin. Chir. **71**:570-573 (Dec.) 1910.

40. Wangensteen, O. H.: On the Significance of the Escape of Sterile Bile into the Peritoneal Cavity, Ann. Surg. **84**:691-702 (Nov.) 1926.

41. Nauwerck, C., and Lübke: Gibt es eine gallige Peritonitis ohne Perforation der Gallenwege? Berl. klin. Wchnschr. **50**:624-627 (April 7) 1913.

42. Blad, A.: Studien ueber Gallenperitonitis ohne Perforation der Gallenwege, Arch. f. klin. Chir. **109**:101-120, 1917.

43. Risel: Zur Frage der sogenannten galligen Peritonitis ohne Perforation der Gallenwege, Deutsche med. Wchnschr. **40**:1599-1600 (July 30) 1914.

cystitis and Kubig's<sup>44</sup> case of volvulus of the gallbladder, in which, in spite of total necrosis of the mucosa, submucosa and muscularis, no bile was found in the peritoneal cavity. Andrews and Aronsohn<sup>45</sup> more recently found that bile peritonitis developed in about one ninth of their dogs after the injection of small amounts of bile salts into the gallbladder by a retrograde catheter inserted up the common duct. In these dogs there was no evidence of perforation of the gallbladder or of the bile ducts. Combined bile salts were found to be less active in this regard than unconjugated solutions, and it is possible that deconjugating enzymes may be a factor in producing leakage.

*Toxicity of Bile.*—Early experimental work on bile peritonitis indicated that the toxic action of absorbed bile might be the chief lethal factor. Wangenstein stated that "the experimental animal dies of cholemia due to the toxic action of the bile." In dogs with experimental bile peritonitis he noted reddening of the peritoneal surfaces but made no mention of any exudate. In dogs dying of bile peritonitis Ziegler and Orr<sup>46</sup> found an increase in the nonprotein nitrogen and the urea nitrogen content of the blood, which they attributed to an increase in the destruction of tissue, and a fall in the chloride content of the blood, which they attributed to vomiting. They found the peritoneal cavity distended with "bile-stained liquid" but made no other mention of its nature. Aerobic cultures were positive in one case and negative in four cases. Horrall<sup>46</sup> gave an extensive review of work on the toxicity of bile. He reported by experiments on heart-lung preparations that bilirubin is a nontoxic substance. Still<sup>47</sup> also stated that bilirubin is nontoxic. Regan and Horrall<sup>48</sup> showed that dehydrocholic acid is not as toxic as glycocholic acid. Andrews, Thomas and Schlegel<sup>49</sup> placed bits of liver in the pleural cavities and in the axillae of dogs and attributed the ensuing death to toxic reaction from the implant. Rewbridge and

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44. Kubig, G.: Ueber Volvulus der Gallenblase, München. med. Wchnschr. **59**:1998-2000 (Sept. 10) 1912.

45. Andrews, E., and Aronsohn, H. G.: Relative Toxicity of Different Bile Salts on the Normal Gall Bladder, Proc. Soc. Exper. Biol. & Med. **34**:765-767 (June) 1936.

46. Horrall, O. H.: Bilirubin, a Non-Toxic Substance: Experimental Study of Bilirubin in Heart-Lung Preparations, J. Lab. & Clin. Med. **14**:217-224 (Dec.) 1928; The Toxicity of Bile, Physiol. Rev. **11**:122-142 (April) 1931; The Toxicity of Bile, University of Chicago Science Series, Chicago, University of Chicago Press, 1927-1928, vol. 6, pp. 287-290. Horrall and Carlson.<sup>29</sup>

47. Still, Eugene U.: On the Toxicity of Purified Bile Preparations, Am. J. Physiol. **88**:728-736 (May) 1929.

48. Regan, J. F., and Horrall, O. H.: The Physiologic Action of Dehydrocholic Acid, Am. J. Physiol. **101**:268-273 (July) 1932.

49. Andrews, E.; Thomas, W. A., and Schlegel, K.: Newer Aspects of Liver Disease, Surg., Gynec. & Obst. **47**:179-182 (Aug.) 1928.



Hrdina,<sup>50</sup> in discussing the etiologic rôle of bacteria in bile peritonitis, produced peritonitis in twenty dogs by allowing bile to drain into the peritoneal cavity. Determinations of bilirubin by the van den Bergh method and of bile salts by the quantitative Pettenkofer test were made on blood drawn from the femoral veins of these dogs four and eighteen hours after operation. No increase in the amount of bilirubin or of bile salts could be detected by these methods, even though the animals were dying as the result of peritonitis. Too much reliance should not be placed on results obtained by the quantitative Pettenkofer test.

*The Rôle of Bacteria in the Production of Bile Peritonitis.*—The literature on this angle of the subject will be reviewed more fully in the next paper of this series. Suffice it to say that certain authors, including Ellis and Dragstedt,<sup>51</sup> Andrews and Hrdina,<sup>52</sup> Rewbridge,<sup>53</sup> Andrews, Rewbridge and Hrdina<sup>54</sup> and Dvorak,<sup>55</sup> have attributed an importance to bacteria in peritonitis due to liver autolysis; Andrews and his co-workers extended this work to bile peritonitis. Other authors, especially Trusler and Reeves<sup>56</sup> and Trusler, Reeves and Martin,<sup>57</sup> are not convinced of the importance of these organisms in the production of bile peritonitis. Still other writers, including Horrall,<sup>58</sup> Ziegler and Orr<sup>30</sup> and Wangenstein,<sup>40</sup> made only aerobic cultures and did not find

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50. Rewbridge, A. G., and Hrdina, L. S.: The Etiological Rôle of Bacteria in Bile Peritonitis: An Experimental Study in Dogs, *Proc. Soc. Exper. Biol. & Med.* **27**:528-529 (March) 1930.

51. Ellis, James C., and Dragstedt, L. R.: Effect of Liver Autolysis in Vivo, *Proc. Soc. Exper. Biol. & Med.* **26**:304-305, 1929; Liver Autolysis in Vivo, *Arch. Surg.* **20**:8-16 (Jan.) 1930.

52. Andrews, E., and Hrdina, L.: Liver Autolysis in Vivo, *Proc. Soc. Exper. Biol. & Med.* **27**:987-988, 1930; The Cause of Death in Liver Autolysis, *Surg., Gynec. & Obst.* **52**:61-66 (Jan.) 1931.

53. Rewbridge, A. G.: The Etiological Rôle of Gas-Forming Bacilli in Experimental Bile Peritonitis, *Surg., Gynec. & Obst.* **52**:205-211 (Feb.) 1931.

54. Andrews, E.; Rewbridge, A. G., and Hrdina, L.: Causation of *Bacillus Welchii* Infections in Dogs by Injection of Sterile Liver Extracts or Bile Salts, *Surg., Gynec. & Obst.* **53**:176-181 (Aug.) 1931; Causation of *B. Welchii* Infection in Dogs with Sterile Liver Extract and Bile Salts, *Proc. Soc. Exper. Biol. & Med.* **28**:136-137, 1930.

55. Dvorak, H. J.: Liver Autolysis in the Peritoneal Cavity of the Dog, *Proc. Soc. Exper. Biol. & Med.* **29**:431-434 (Jan.) 1932.

56. Trusler, H. M., and Reeves, J. R.: Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis: Bacterial Flora of the Liver and Muscle of Normal Dogs, *Arch. Surg.* **28**:479-491 (March) 1934.

57. Trusler, H. M.; Reeves, J. R., and Martin, H. E.: Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis, *Arch. Surg.* **30**:371-393 (March) 1935.

58. Horrall, O. H.: Experimental Bile Peritonitis and Its Treatment in the Dog, *Arch. Int. Med.* **43**:114-128 (Jan.) 1929.

bacteria in the bile or peritoneal fluid. Boyce and McFetridge,<sup>59</sup> in their recent article on the so-called liver death, found that pieces of normal liver of dogs placed intraperitoneally produced death but that incubated liver extract did not, contrary to the results of some of the previous workers. Dvorak<sup>56</sup> concluded on the basis of his experiments on liver autolysis in dogs that anaerobic bacteria or their toxic products cause death or lysis of dog's liver, and he found no toxic product in the liver responsible for death which was inherent to hepatic tissue and independent of bacterial activity.

*Dehydration and Loss of Fluid as a Factor in Bile Peritonitis.*—

Among the many observers who produced experimental bile peritonitis, some<sup>40</sup> made no mention of a peritoneal exudate. Others mentioned the exudate but did not attribute an important rôle to it. Thus in certain of the dogs of Andrews, Rewbridge and Hrdina,<sup>54</sup> 300 cc. of a sero-sanguineous exudate was found in the peritoneal cavity at necropsy. Mason and his co-workers<sup>60</sup> were the first to demonstrate that this fluid might be sufficient in amount to be of serious import. Mason and Lemon stated: "The fluid lost into the abdomen is doubtless sufficient to cause circulatory disturbances; however, we have not been able to prolong life by administering fluids intravenously—the amount of free fluid usually being equal to one-third to one-half of the total blood volume." These authors pointed out the accompanying decrease in the plasma volume and the fibrous deposits on the peritoneal surface, but they did not discuss the effects of loss of protein. They expressed the belief that there are three factors in death due to liver autolysis: (1) the toxic factor, since from 7 to 8 cc. of their liver extract solution<sup>61</sup> injected intravenously produced death; (2) bacilli resembling the Welch bacillus, which are not important, as a culture of them given intraperitoneally did not cause death, and (3) anhydremia with a decrease in the plasma volume. Mason and Davidson<sup>60d</sup> had previously analyzed the peritoneal exudate for nonprotein nitrogen, urea nitrogen, amino-acid nitrogen, sugar and uric acid and found that it contained higher

59. Boyce, F. F., and McFetridge, E. M.: So-Called "Liver Death": A Clinical and Experimental Study, *Arch. Surg.* **31**:105-136 (July) 1935.

60. (a) Mason, Edward C., and Lemon, Cecil W.: Anhydremia as a Possible Cause of Death in Liver Autolysis, *Surg., Gynec. & Obst.* **55**:427-431 (Oct.) 1932; (b) Autointoxication and Shock, *ibid.* **53**:60-64 (July) 1931. (c) Mason, E. C., and Davidson, E. C.: A Study of Tissue Autolysis in Vivo: I. Blood Changes; Physical and Chemical, *J. Lab. & Clin. Med.* **10**:622-630 (May) 1925; II. A Pharmacological Study of the Toxic Material, *ibid.* **10**:906-913 (Aug.) 1925. (e) Mason, E. C.; Davidson, E. C., and Matthew, C. W.: A Study of Tissue Autolysis in Vivo: III. Observations Using the Spleen, *ibid.* **10**:997-999 (Sept.) 1925. (f) Mason, E. C., and Nau, C. A.: The Cause of Death Due to Liver Autolysis, *Surg., Gynec. & Obst.* **60**:769-774 (April) 1935.

amounts of all these components, except sugar, than the circulating blood. In this article they discussed the exudate entirely from the standpoint of its potential toxic properties. Mason, Davidson and Matthew<sup>60e</sup> later showed that spleen autolysis produces a picture quite similar to that of liver autolysis. Horrall<sup>58</sup> also noted blood-stained fluid in the abdomen of dogs dying of biliary peritonitis but did not analyze it for protein content. Mason and Nau,<sup>60f</sup> in their recent review of the cause of death due to liver autolysis, reported that the anaerobic bacillus found at the time of death may be injected intraperitoneally and intravenously into animals without causing any harmful results. In this article they placed less emphasis on the baneful effects of the accompanying anhydremia and revert to their former point of view as to the prime importance of the absorption of toxic products generated from the hepatic tissue. Blalock<sup>31</sup> produced bile peritonitis in nineteen dogs. In one of these the hematocrit reading rose from 41 to 61.7 per cent, and autopsy revealed the presence of 265 cc. of blood-tinged fluid in the peritoneal cavity and considerable reddening of the serous surfaces. He suggested that the loss of this fluid might be a factor in the production of shock, but he did not analyze the fluid for protein content. Trusler, Reeves and Martin<sup>57</sup> noted the presence of peritoneal exudate in dogs dying of peritonitis due to liver autolysis or to the injection of bile salts. In several of their dogs there was 500 cc. of blood-tinged fluid in the abdomen. They reported no analysis of this fluid for protein content and made no statement as to the importance of the loss of this much fluid from the circulating blood volume in a short time. They were chiefly interested in the bacterial content of the exudate.

A study of these reports on peritonitis due to liver autolysis and to the injection of bile or bile salts led us<sup>61</sup> to believe that the mere physical loss of fluid into the peritoneal cavity might be one of the lethal factors in this condition. At the same time we made further studies on the bacterial factor in bile peritonitis, which are to be included in another paper in this series. The experiments on the surgical shock factor in bile peritonitis are listed here.

#### EXPERIMENTAL STUDY

In all experiments dogs under complete anesthesia and free from all pain were used. In certain experiments dogs recovering from a sterile surgical operation were kept in comfortable cages with an adequate supply of food and water, while in other instances the dogs were killed painlessly at the termination of the experi-

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61. Harkins, H. N.; Harmon, P. H.; Hudson, J., and Andrews, E.: *Mechanism of Death in Bile Peritonitis*, Proc. Soc. Exper. Biol. & Med. **32**:691-693, 1935.

ment. Certain dogs were given intravenous medication without anesthesia in the same manner as performed on man and suffered no pain. Eighty-five dogs were used in this study as well as numerous rabbits, cats, pigeons and guinea-pigs.

GROUP 1.—*Fall in Blood Pressure.*—The technic used for producing bile peritonitis in all groups of experiments was essentially the same and will be described at this point. In some experiments repurified Armour's bile salts were made into a 10 per cent aqueous solution and autoclaved in Erlenmeyer flasks; in others, whole bile was used. This was obtained by aspiration with a syringe and needle of the gallbladder of normal living animals under ether anesthesia, aseptic surgical technic being used. The bile was cultured aerobically and anaerobically, and all contaminated specimens were discarded. In other experiments bile peritonitis was produced by defundation of the gallbladder combined with ligation of the common duct. Sodium barbital, 250 mg. per kilogram of body weight, was injected intramuscularly into the thigh in most experiments. In certain experiments the blood pressure was recorded on a drum with a cannula in the carotid artery. Clean, but not aseptic, technic was used in injecting the sodium barbital and in cannulating the carotid artery. The abdomens of the animals were shaved when anesthesia was complete, and after double sterilization of the skin with iodine and with careful aseptic surgical technic, the abdomen was opened and the bile or bile salts introduced under direct vision. In most instances the incision was made in the linea alba to avoid touching the muscles of the abdominal wall. In other instances, in which a rectus incision was used, the end of the syringe and the bile were not allowed to come directly in contact with the muscle. The wounds were closed in layers, and the animals were observed, the blood pressure being taken at frequent intervals. After the blood pressure had fallen to a so-called shock level (70 mm. of mercury), the abdomen was again opened in certain instances, aseptic surgical technic being used. Sometimes the second incision removed the wound of the first, and at other times the incisions were entirely separate. The material from the peritoneal cavity was then cultured, aspiration being performed with a multi-perforated stainless steel suction tip, and in some instances the cavity was washed out two or three times with sterile physiologic solution of sodium chloride. The abdomen was reclosed in those animals that were still living.

The blood pressure sometimes fell slightly at the time of injection of the bile but soon returned to the control value. This occasional initial fall is similar to that seen in so-called primary shock, which is accompanied by no marked decrease in cardiac output or blood volume, as shown by Blalock.<sup>62</sup> After this the blood pressure fell gradually until the animal was near death, at which time there was believed to be a rapid failure of the mechanism which compensates for the decrease in blood volume. This was evidenced by the rapid fall in the blood pressure. The blood pressure fell in ten of fourteen animals in which it was recorded to below 70 mm. of mercury. In the remaining instances the record of the blood pressure was not continued until death. The fall in blood pressure occurred in animals with peritonitis due to injection of 10 per cent solution of bile salts or whole gallbladder bile and

62. Blalock, A.: Effects of Primary Shock on Cardiac Output and Blood Pressure, *Proc. Soc. Exper. Biol. & Med.* **31**:36-37, 1933; footnote 19.

to defundation of the gallbladder with ligation of the common duct. Blood pressure tracings are shown in charts 1 and 2, which are typical except that the final collapse of blood pressure is not present. The later fall in blood pressure is similar to that seen in animals in secondary shock after trauma to an extremity,<sup>6</sup> intestinal manipulation,<sup>11</sup> burns,<sup>7</sup> etc., which is accompanied by a decrease in the cardiac output and the blood volume.<sup>10</sup>

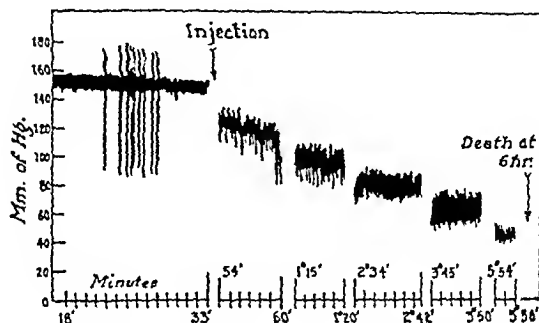


Chart 1.—Tracing showing the fall in blood pressure after the intraperitoneal injection of 105 cc. of a 10 per cent solution of bile salts (7.5 cc. per kilogram of body weight) in dog A, which weighed 14 Kg. The initial reading was 152 mm. of mercury, and the final reading ten minutes before death was 45 mm. The kymographic drum was stopped several times during the recording of the tracing.

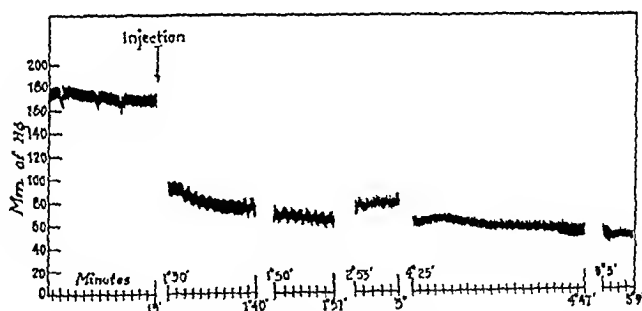


Chart 2.—Tracing showing the fall in blood pressure after the intraperitoneal injection of a 10 per cent solution of bile salts (7.5 cc. per kilogram of body weight) in dog B, which weighed 8.5 Kg. The final reading of 45 mm. of mercury was obtained three minutes before the animal was killed by bleeding.

GROUP 2.—*Blood Concentration.*—The percentage of hemoglobin was determined by the Sahli hemoglobinometer and the hematocrit reading by the Van Allen hematocrit. The ear was shaved, and a sample of blood was obtained from a large vein by cutting with a razor. Except when secondary shock was present, the flow of blood was free enough to require a compressive dressing after the reading was obtained. This method was considered to assure a uniform sample without danger of low counts because of separation of the cells to the center of a capillary axial stream. Readings were taken before the intraperitoneal injection and at intervals thereafter until death.

The percentage of hemoglobin and the hematocrit reading rose gradually, as shown in chart 3. The greatest increase was in experiments LL, MM and NN, in which the percentage of hemoglobin rose from 101, 118 and 108 to 177, 190 and 178, and the hematocrit reading, from 51, 50 and 51 to 80, 77 and 80, respectively. All of the thirty-two dogs in which the blood concentration was carefully followed after the institution of bile peritonitis showed a definite rise in the percentage of hemoglobin and in the hematocrit reading. Control experiments on dogs under similar anesthesia showed little or no blood concentration. The concentration began soon after the onset of the peritonitis and increased gradually in contrast to the blood pressure, which remained fairly well compensated until near the end, when it collapsed suddenly. This is similar to the changes in the blood concentration and in the blood pressure in burns, as was shown by Harkins.<sup>9</sup> It indicates that observations on the concentration of the red cells might be of more clinical value than observations on the blood pressure. Accompanying the concentration of the blood there was a noticeable difficulty in obtaining samples of blood from the veins and arterioles of the ear. A cut directly over a vessel that at the start of the experiment would have given a good flow of blood would bleed very scantily, even though the blood pressure had not fallen appreciably. This difference was more than the mere increase in the viscosity of the blood could account for and was taken as evidence for the compensatory vasoconstriction secondary to a diminution in the blood volume. Possibly, as Freeman<sup>23</sup> suggested, this is due to an increase in the output of epinephrine.

**Group 3.—Loss of Fluid into the Peritoneal Cavity.**—In most experiments the peritoneal cavity was opened immediately after death, and the amount of peritoneal fluid was measured. In other experiments the peritoneal fluid was removed sometime before death and again after death. There were twenty-seven experiments in this group.

In four experiments in which the animal was killed by bleeding after the production of bile peritonitis, the amount of peritoneal exudate averaged 1.8 per cent of the body weight. In ten experiments in which the amount of fluid was determined at death, it averaged 1.8 per cent of the body weight. In eleven experiments in which the peritoneal cavity was aspirated and the animal treated by a transfusion of blood or infusion of plasma with usually ultimate death, the total amount of peritoneal fluid averaged 3.5 per cent of the body weight. Two other animals are included in the twenty-seven listed in table 1. The greater average amount of peritoneal fluid found in the treated animals indicates a possible prolongation of life, permitting greater loss of fluid or direct leakage of the plasma used as intravenous medication into the peritoneal cavity. The average total amount of peritoneal exudate for the twenty-

seven animals was 2.5 per cent of the body weight. To be strictly accurate, the amount of bile or bile salts originally injected into the peritoneal cavity should be deducted. In the twenty-seven experiments this averaged 0.4 per cent of the body weight, and thus the corrected value for the amount of peritoneal fluid would be 2.1 per cent of the body weight.

This amount of peritoneal fluid is of especial significance when it is considered, as will be shown later, that it is not a mere transudate but is chemically similar to blood plasma. The average amount of peritoneal fluid found in these experiments is slightly less than that of edema fluid found by us in cases of shock due to freezing,<sup>10</sup> in which it averaged 2.5 per cent of the body weight, or of shock due to burns,

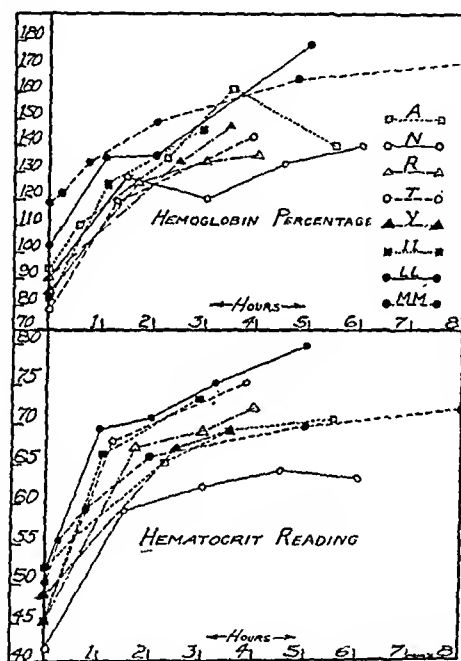


Chart 3.—Curves showing the rise in the percentage of hemoglobin and in the hematocrit readings in animals with bile peritonitis. Animals A and N received intraperitoneal injections of 7.5 and 2.5 cc. of a 10 per cent solution of bile salts per kilogram of body weight, respectively. Animals R, T, Y and MM were given 5 cc. of a 10 per cent solution of bile salts per kilogram of body weight. Animals II and LL received 4 and 5 cc. of whole gallbladder bile per kilogram of body weight. A rise in the percentage of hemoglobin and in the hematocrit readings was found in twenty-four other animals data for which are not shown in this figure.

in which it averaged 2.2 per cent of the body weight. However, the average amount of fluid reported in the present experiments includes values obtained on several animals that did not die, and furthermore it is possible that the correction applied for the amount of bile or bile salts originally injected is too rigid, as some of the injected solution

TABLE 1.—Measurement of Peritoneal Exudate in Twenty-Seven Dogs \*

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\* The amount of 10 per cent solution of bile salts or of whole gallbladder bile injected intraperitoneally is given in the third column. The extent of the exen-  
tration of blood before death or treatment is given, followed by the time interval before said death or treatment at which time the peritoneal exudate was removed  
and measured. One animal (BB) recovered without treatment other than aspiration. The final column includes the amount of peritoneal fluid aspirated both before  
died, and additional aspiration of the peritoneal cavity was done post mortem. The final column includes the amount of peritoneal fluid aspirated both before  
treatment and post mortem in those instances in which two aspirations were performed.



may have been absorbed. Incomplete evidence for this is that the chemical constitution of the peritoneal fluid so closely resembled blood plasma.

Some interesting calculations can be made from the change in hematocrit readings and the amount of peritoneal exudate. In table 1 it is seen that the average initial hematocrit reading was 47 and the average reading at the time of the first removal of peritoneal fluid was 67. Assuming a constant value for the erythron, that the amount of peritoneal fluid found escaped directly from the blood stream as blood plasma, reducing the blood volume by that amount, and that the blood volume is one thirteenth of the body weight, then on the basis of the initial hematocrit reading a theoretical final hematocrit reading can be calculated. Thus, with the average weight 11.1 Kg.,<sup>63</sup> the blood volume is 855 cc. Since the initial hematocrit reading is 47, 402 cc. of this will be cells and 453 cc. plasma. If an average of 212 cc.<sup>63</sup> is lost into the peritoneal cavity, the final plasma volume will be 241 cc., which, with a constant value for the erythron, would correspond to a final theoretical hematocrit reading of 62. Since the actual final hematocrit reading is 67, this means that only 75 per cent of a theoretical reduction in blood volume calculated on the basis of hematocrit readings is accounted for by the peritoneal fluid. Possibly, as Swingle and his associates<sup>24</sup> have postulated, there is a general escape of fluid from the entire vascular system. It is to be realized, of course, before giving these calculations too much value, that they are based on several assumptions and on figures that include a large experimental error.

It is quite possible that not only the amount of fluid lost from the blood stream but the interval of time in which it is lost may be a factor. It is a well known fact that the body can tolerate large losses of exudate over a sufficiently long period of time. Enormous collections of fluid in nephritis are an example. On the other hand, the amount of plasma or blood lost per hour would not be an adequate index of the severity of the leakage, as an average-sized man could stand the loss of 1,000 cc. of blood in one hour better than 500 cc. of blood every hour for four hours. In three experiments in which the animal did not die immediately (MM, NN and DD), the peritoneal fluid obtained at the first aspiration represented an average of 1.1, 7.2 and 12.1 cc. per kilogram of body weight per hour. In four other experiments (A, V, EE and L) the amount of fluid obtained at death represented an average of 4.8, 4.8, 4.7 and 1.9 cc. per hour. In three experiments in which shock was produced by burns,<sup>9</sup> the edema fluid (experiments 5, 4 and 8) represented an average of 1, 4.7 and 4.6 cc. per kilogram per hour. In

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63. The averages of 11.1 Kg. for the weight of the dogs and 212 cc. for the amount of peritoneal fluid differ slightly from those given in table 1 because they do not include those from Experiment GG, in which no hematocrit determinations were made and which hence should not be included in the averages.

three experiments in which shock was produced by freezing,<sup>10</sup> the edema fluid (experiments 1, 5 and 10) represented an average of 2, 2 and 1.4 cc. per kilogram per hour. These figures vary considerably but are of the order of 5 cc. per kilogram per hour. They seem to be of the same magnitude in shock whether due to bile peritonitis, burns or freezing. It is to be noted that 5 cc. per kilogram per hour represents only 350 cc. per hour in a man weighing 70 Kg. These calculations concerning the fluid lost per hour are of little value at present because of the extreme variation of the results, but they may serve as a basis for future studies along this line.

GROUP 4.—*Loss of Fluid into the Viscera and Lumen of the Bowel.*—Because of the uniform finding of extensive subserosal hemorrhage and occasional hemorrhage into the lumen of the bowel in cases of experimental bile peritonitis, it was believed that this loss of blood might be an added lethal factor. No way of measuring the hemorrhage beneath the parietal peritoneum was found. To determine that into the bowel, the following experiments were performed. The bowel was removed from the pylorus to the region of the peritoneal reflection of the rectum after ligation at the upper and lower ends so as to prevent loss of contents. It was then weighed after all the mesentery had been carefully removed. In table 2 this weight is listed as the weight of the intestine when full. The bowel was then split lengthwise, and the contents were washed away. In many instances these contents were definitely blood-stained. The bowel was then dried in a uniform manner by patting with a dry towel. It was then weighed and its length measured after laying it lengthwise on the floor, serous surface down. A solid portion, usually about 3 Gm. of the wall of the bowel 30 cm. from the pylorus, was then placed in a weighed beaker and evaporated to constant weight at 113 C. from forty to forty-eight hours.

These observations were made on ten animals after the injection intraperitoneally of bile salts, on six animals after the injection intraperitoneally of bile from the gallbladder and on twelve control animals. The intestinal lengths were measured because it was early noted that in individual animals the ratio of intestinal length to body weight was not constant. However, it is seen that in the three series of experiments shown in table 2 the average length of the intestine per kilogram of body weight was 34, 35 and 32 cm., respectively. The average weight of the full intestine per kilogram of body weight was 32, 31 and 31 Gm.; these figures represent remarkably constant results. The weight of the contents of the intestine was definitely higher in the series of animals with bile peritonitis (6.7 and 6.6 Gm. per kilogram of body weight) than in the control animals (3.9 Gm. per kilogram). This is in spite of the fact that anesthesia and preanesthetic feeding and the administration of fluid were the same in the series with peritonitis as in the control series. The difference of 3.7 Gm. per kilogram of the body weight is only 0.37 per cent of the body weight, which is of minor importance compared to the amount of peritoneal exudate (order of 2 per cent of the body weight). In certain cases there was a definite

bloody diarrhea, but the amount of bloody feces lost was never more than 100 Gm. The solid content of the bowel after evaporation to dryness in the series of animals with bile peritonitis averaged 0.175 Gm. per gram, which was definitely less than in the control series, but, on the other hand, in the series in which whole bile was used the average was

TABLE 2.—*The Effect of Bile Peritonitis on the Fluid Content of the Wall and the Lumen of the Bowel \**

Experiment	Weight of Dog, Kg.	Length of Intestine, Cm.	Weight of Full Intestine, Gm.	Weight of Empty Intestine, Gm.	Weight of Intestinal Contents, Gm.	Dried Solids of Intestinal Wall, Gm.
Intraperitoneal Injection of Bile Salt						
AA.....	6.8	...	194	176	18	0.188
CC.....	10.8	...	440	329	111	0.187
Y.....	7.5	...	319	302	17	.....
GG.....	18.5	518	734	440	294	0.191
HH.....	16.5	518	552	414	138	0.188
DD.....	7.0	337	257	205	52	0.189
V.....	13.0	...	400	265	135	.....
X.....	10.0	...	177	149	28	.....
MM.....	20.0	394	536	385	151	0.236
NN.....	14.5	350	383	292	96	0.043
Average.....	12.5	423	400	316	84	0.175
Average Kg.	....	34	32	25	6.7	
Intraperitoneal Injection of Gallbladder Bile						
II.....	7.5	355	281	190	91	0.207
EE.....	13.2	420	416	309	107	0.181
FF.....	13.5	402	333	264	69	0.345
KK.....	6.5	290	198	189	9	0.208
LL.....	12.0	363	397	327	70	0.330
PP.....	....	...	...	...	..	0.095
Average.....	10.5	366	325	256	69	0.228
Average Kg.	....	35	31	24	6.6	
Control Experiments						
FFF.....	8.0	324	266	243	23	0.200
GGG.....	8.8	345	339	313	26	0.202
HHH.....	23.0	395	448	371	77	0.212
III.....	10.8	383	424	345	79	0.195
JJJ.....	7.2	...	221	216	5	0.182
KKK.....	13.0	...	456	419	37	.....
W.....	21.5	...	490	430	60	.....
PPP.....	5.0	330	230	204	26	0.206
LLL.....	6.5	300	194	157	37	0.237
MMM.....	4.8	277	322	277	45	0.226
NNN.....	9.5	300	254	210	44	0.309
OOO.....	5.8	275	186	162	24	0.196
Average.....	10.3	326	319	279	40	0.216
Average Kg.	....	32	31	27	3.9	

\* The experiments for the injection of bile salts and whole bile are listed separately and are followed by the control experiments. It is seen from the next to the last column to the right that the intestinal contents of the dogs with peritonitis averaged slightly more than that of the controls. In the last column to the right it is seen that the solid content of the wall of the intestine was less in the experiments in which bile salts were used than in the control experiments, but that it was greater in the experiments in which whole bile was used than in the control experiments.

higher than in the control series. Hence, the investigation of the water content of the tissue of the wall of the bowel gave no striking results. In conclusion, it seems that the amount of measurable fluid and blood lost into the viscera and intestinal lumen is a minor factor in the production of shock in bile peritonitis.

GROUP 5.—*Bleeding Volume*.—After the blood pressure had reached a so-called shock level (about 70 mm. of mercury), the animal, which was lying in a supine position, was tipped so that the feet were elevated 10 degrees and bled to death from the right carotid artery. After the blood had stopped flowing, the other carotid artery was opened, and the animal tipped up to an angle of 75 degrees, but these additional procedures usually yielded less than 10 cc. more blood.

The bleeding volume in four animals averaged 1.8 per cent of the body weight, as shown in table 3. The bleeding volume was determined in experiment M to be 490 cc. (weight of dog, 12.2 Kg.; peritonitis produced by 2 cc. of whole bile per kilogram of body weight; bleeding done twenty-one hours after the institution of peritonitis), which corresponds to 4 per cent of the body weight. The results in this experiment are not included in the averages because there was little evidence of blood concentration, the percentage of hemoglobin rising only from 89 to 93 and the hematocrit reading from 42 to 49, and the total volume of peritoneal exudate at death was only 65 cc. (0.5 per cent of the body weight). The bleeding volume was determined in experiment X by the method of Blalock<sup>64</sup> (evisceration with measurement of the blood left in peritoneal and pleural cavities) as 0.75 per cent of the body weight, but as this reading was taken some time (less than three hours) after death, and since Blalock does not state the relationship of his determinations to the time of death, this reading is not included in the averages. Blalock<sup>64</sup> found the volume of bleeding as expressed in percentage of body weight and determined by his method to be as follows in the different types of experiments: (1) control, 5.93; (2) ether control, 4.23; (3) sodium barbital control, 5.23; (4) injection of histamine, 3.56; (5) injection of acetylcholine, 3.46; (6) increased intrapericardial pressure, 4.74; (7) hemorrhage, 1.4, and trauma to an extremity, 1.73. Using the method adopted in the present paper, Roome, Keith and Phemister<sup>14</sup> showed that in experimental shock due to hyperventilation, anaphylaxis, administration of histamine, section of the spinal cord, and spinal anesthesia, the bleeding volume averaged 3.8 per cent of the body weight. This is only slightly less than the average of 4.5 which they determined and 4.1 which Harkins<sup>65</sup> determined for control animals. On the other hand, in shock due to trauma to an extremity, hemorrhage, plasmapheresis and intestinal manipulation, the bleeding volume, according to Roome, Keith, and Phemister, was greatly reduced, averaging 1.7 per cent. Harkins<sup>65</sup> found the bleeding volume in burns to average 1.6; Harkins and Harmon<sup>10</sup> found it to average

64. Blalock, A.: Shock: Further Studies with Particular Reference to the Effects of Hemorrhage, *Arch. Surg.* **29**:837-857 (Nov.) 1934.

65. Harkins, H. N.: The Bleeding Volume in Severe Burns, *Ann. Surg.* **102**: 444-454 (Sept.) 1935.

2.7 in experimental freezing, and Harmon and Harkins<sup>66</sup> found it to average 3.3 in experimental intoxication due to the colon bacillus.

Blalock<sup>31</sup> stated that in his experiments with production of peritonitis by bile, pancreatic juice or gastric juice, he found relatively little early reduction in cardiac output. Since the cardiac output, blood volume and bleeding volume are all so intimately related, this work of Blalock's might be considered to be in opposition to our findings. However, Blalock discussed all his experiments together and did not state specifically the amount of reduction in the cardiac output found in bile peritonitis. Furthermore, his doses of bile were less potent than ours, as gaged by their effect on blood concentration. It is unlikely that there would be reduced cardiac output in this type of experiment without an accompanying blood concentration. Finally, toward the end of Blalock's exper-

TABLE 3.—*Bleeding Volume in Dogs with Bile Peritonitis\**

Ex- peri- ment	Weight of Dog, Kg.	Dose per Kg. of Body Weight	Hours Before Death	Perito- neal Exu- date, Cc.	Hemoglobin Percentage			Hematocrit Reading			Bleed- ing Vol- ume,	Bleeding Volume, Percentage of Body Weight
					Start	Maxi- mum	Rise	Start	Maxi- mum	Rise		
B	8.5	7.5 cc. 10% bile salt	5	178	62	135	73	45	66	21	45	0.5
D	15.5	2.5 cc. 10% bile salt	5½	390	93	138	45	44	70	26	390	2.5
LL	12.0	5.0 cc. whole bile	5	260	101	177	76	51	80	29	210	1.7
KK	6.5	5.0 cc. whole bile	3	65	98	128	30	54	68	14	165	2.5
Average.....												1.8

\* Two of the animals received injections of bile salts intraperitoneally, and two received injections of whole bile intraperitoneally. Bleeding from the carotid artery was done from three to five and one-half hours after the institution of peritonitis, and at necropsy from 65 to 390 cc. of plasma-like peritoneal exudate was found in the peritoneal cavity. A marked rise in the hemoglobin percentage and hematocrit reading was noted in all animals. The bleeding volume is expressed as percentage of the body weight.

iments there was a definite lowering of the cardiac output and "the subsequent change consisted of a greater drop in the cardiac output than in the blood pressure, as is found in secondary shock."

A perusal of the results in the present article on bleeding volume indicates that in control animals and in all those conditions that give rise to so-called primary shock, the bleeding volume is greater than 3 per cent of the body weight. In those conditions that lead to so-called secondary shock, the bleeding volume is less than 3 per cent. The average bleeding volume in bile peritonitis was 1.8 per cent, and according to this criterion comes under the province of secondary shock.

GROUP 6.—*Chemical Analysis of Peritoneal Exudate.*—In thirty-one experiments in which bile peritonitis was produced, a chemical analysis of the peritoneal exudate was made. The fluid was slightly tinged with blood, but clotted if no

66. Harmon, P. H., and Harkins, H. N.: Bleeding Volume in Experimental Colon Bacillus Intoxication, *Proc. Soc. Exper. Biol. & Med.* **32**:1144-1146, 1935.

anticoagulant was added. A similar amount of anticoagulant was added to the peritoneal exudate and to samples of blood obtained from the femoral vein. Analyses were made on the fluid and on the blood plasma. The sugar was determined by the Folin 1929 modification method on a sulfate-tungstate filtrate; the sodium chloride, by the Eisenman open-Carius method; the protein, by the Koch-McMeekin micro-Kjeldahl method, and the nonprotein nitrogen, by the same method on a Folin-Wu filtrate. In certain experiments the albumin-globulin ratio was determined.

Some of the results are shown in table 4. The concentration of sugar is in general lower in the fluid than in the blood plasma. The chloride concentration is approximately the same in the blood plasma and the peritoneal fluid. The nonprotein nitrogen content was often much higher in the fluid than in the blood plasma. The amount of protein in the fluid was often slightly lower than that in the blood plasma but was of the same general order. The albumin-globulin ratio was generally higher in the fluid than in the blood plasma and was often lower in the blood plasma taken at the end of an experiment than that taken from the same animal before the institution of the peritonitis. This was considered to indicate relatively greater leakage of albumin than of globulin into the peritoneal cavity. The extremely low values for sugar in certain of the peritoneal exudates are of interest and may be comparable to the low sugar values in the spinal fluid in meningitis. In experiments in which the blood plasma was analyzed before and after the institution of peritonitis there was usually a slight decrease in the amount of sugar, the total amount of protein, the sodium chloride content and the albumin-globulin ratio. Control determinations on the bile salt solution used in producing peritonitis showed it to give a value of 18.5 mg. per hundred cubic centimeters for sugar content by means of the same method used in the other analyses. The sodium chloride content in the control series was 157 mg. per hundred cubic centimeters; the nonprotein nitrogen content was 41 mg. per hundred cubic centimeters, and the total protein content was 0.57 Gm. per hundred cubic centimeters. The presence of a small amount of protein indicates the uncertainty of the analysis due to colloidal precipitates in the bile salt solution, since the solution was prepared to be protein-free. The high value for nonprotein nitrogen in the control series may explain some of the high values obtained for this component in the blood plasma and peritoneal exudate. These results indicate that there are slight chemical changes in the blood in bile peritonitis, as listed here, but that, more important, the fluid lost into the peritoneal cavity is chemically quite similar to blood plasma. Hence, loss of this amount of plasma-like fluid is much more harmful to the animal than the loss of a similar amount of merely watery fluid.

GROUP 7.—*Pathologic Examination.*—All animals used were subjected to careful autopsy. In addition to an extensive peritoneal exudate (group 3) and hemorrhages into the viscera and lumen of the bowel and beneath the serous surfaces of the peritoneal cavity (group 4), several other observations were made. In certain instances there was a small amount, 20 cc. or less, of pleural exudate. This fluid

TABLE 4.—*Comparison of Chemical Composition of Peritoneal Exudate and Blood Plasma in Experimental Bile Peritonitis \**

Ex- peri- ment	Peritoneal Exudate					Blood Plasma				
	Sugar, Mg. per 100 Cc.	Sodium Chloride, Mg. per 100 Cc.	Non- protein Nitrogen, Mg. per 100 Cc.	Total Protein, Gm. per 100 Cc.	Albumin- Globulin Ratio	Sugar, Mg. per 100 Cc.	Sodium Chloride, Mg. per 100 Cc.	Non- protein Nitrogen, Mg. per 100 Cc.	Total Protein, Gm. per 100 Cc.	Albumin- Globulin Ratio
A	...	615	64	3.9	...	...	656	...	4.6	...
B	60	516	32	4.3	...	...	649	53	2.9	...
C	103	645	50	4.2	3.2	133	623	49	3.9	5.2
D	146	672	39	4.2	4.1	123	606	90	12.5	1.6
E	...	625	27	4.0	4.7	...	...	...	...	...
F	...	683	84	3.7	3.6	...	664	...	4.3	...
G	...	...	115	4.1	6.7	...	621	106	4.0	2.2
H	26	571	...	5.0	3.3	...	531	...	7.7	1.6
I	49	630	83	5.5	8.0	...	563	...	7.8	2.4
L	144	647	43	3.6	2.5	...	...	...	...	...
N	76	643	52	5.7	3.4	0	624	65	6.3	1.9
N	...	622	...	5.7	...	...	...	...	...	...
P	0	628	68	4.0	1.8	...	...	...	...	...
P	0	570	289	5.5	...	...	...	...	...	...
R	310	646	85	4.6	2.0	...	...	...	...	...
T	69	664	40	4.1	2.5	...	...	...	...	...
T	0	373	213	6.3	4.0	...	...	...	...	...
V	51	674	55	4.4	2.6	...	...	...	...	...
X	82	652	59	3.9	1.4	...	...	...	...	...
X	119	690	39	3.8	2.6	...	...	...	...	...
AA	0	619	223	5.5	...	...	...	...	...	...
BB	162	646	31	2.4	...	...	...	...	...	...
CC	253	633	143	2.0	...	...	...	...	...	...
CC	0	598	110	2.2	...	...	...	...	...	...
DD	97	652	143	3.6	10.0	...	...	...	...	...
DD	0	617	181	5.0	3.2	...	...	...	...	...
EE	121	663	47	4.3	1.2	...	...	...	...	...
FF	217	652	40	3.5	1.3	...	...	...	...	...
FF	0	557	113	4.3	2.7	...	...	...	...	...
KK	117	646	117	3.9	4.6	89	621	54	4.4	4.8
LL	154	623	60	3.5	9.3	0	573	51	3.8	3.6
MM	130	612	74	3.7	3.1	86	619	32	5.9	2.5
MM	0	605	100	5.0	2.1	...	...	...	...	...
NN	107	529	57	4.4	2.1	153	649	30	5.7	1.5
NN	0	630	64	5.3	4.0	...	...	...	...	...

\* In the column of analyses of the peritoneal exudate, in nine instances a sample of peritoneal fluid was collected several hours after the injection of bile or bile salts, and a second analysis was made from fluid collected later at necropsy. The analyses of blood plasma given represent the results on samples of blood collected some time after the injection of bile or bile salts. In two experiments, KK and LL, control blood analyses before the start of the experiment gave values of 109 and 109 mg. for sugar, 582 and 610 mg. for the sodium chloride, 36 and 29 mg. for the nonprotein nitrogen, 5.0 and 6.2 Gm. for the total protein, and 3.1 and 8.6 for the albumin-globulin ratio, respectively. The table shows essentially that the peritoneal exudate is grossly similar to blood plasma in chemical composition. In most instances the blood samples were taken shortly before the death of the animal.

contained protein in almost the same concentration as blood plasma. The lungs were engorged with blood in the dependent portions in some instances. The liver, spleen and kidneys were grossly normal. There was no thickening of the wall of the gallbladder. In many instances, especially when the blood pressure had remained low for some time, there was a hemorrhagic infiltration of the mesenteric glands, especially those in the cecal region, and in the medulla of the adrenal

glands. Gross examination revealed no change in the adrenal cortex. In rare instances there was an apparently chronic enlargement of the thyroid gland. In no instance of a profound fall in the blood pressure was there an engorgement of the large mesenteric vessels, and the peripheral arteries and veins seemed to be collapsed. No abnormal intravascular clotting was noted, and the heart seemed to be normal in all instances. Examination of the stomach and duodenum showed no ulceration similar to a Curling ulcer, although in several instances there was a localized effusion of blood beneath the mucosa. There was marked fat necrosis present in the peritoneal cavity in most instances in which bile peritonitis had existed for more than six hours. This was found in the fat around the pancreas and remote points as well.

Microscopic examination showed hemorrhages into the subserosa and submucosa of the intestinal wall. In the adrenal glands there were hemorrhages under the capsule in the glomerular layer and especially at the corticomedullary junction in the reticular and fascicular zones with necrosis of the cells of the medulla. Necrosis and hemorrhage in the germinal centers of the mesenteric lymph glands were found. The lungs were normal except for occasional areas of edematous fluid in the alveoli and small hemorrhages.

Most of the positive evidence found at necropsy can be explained on the basis of the irritative local action of the bile or bile salts. These changes include the exudative and hemorrhagic alterations in the viscera and peritoneal cavity. The absence of thickening of the wall of the gallbladder is said by Blalock to militate against the presence of histamine in the blood stream. The presence of certain of the hemorrhagic changes in the viscera, especially in the medulla of the adrenal glands, mesenteric glands and intestinal lumens, has been noted in shock from other causes. Brooks and Blalock<sup>26</sup> noted somewhat similar changes in shock due to trauma or to simple hemorrhage. They found that barbital or ether anesthesia alone can cause certain of these changes. Similar observations have been made by Fender,<sup>67</sup> Bardeen<sup>68</sup> and others in burns. Donahue and Parkins<sup>69</sup> studied the changes in the adrenal cortex after trauma. These authors found that hemorrhages appeared in the adrenal cortex of dogs four or more hours after trauma and that the severity of this hemorrhage was dependent on the degree of trauma. Hemorrhagic areas and a depletion of lipoids were generally confined to the reticular and fascicular zones. These authors expressed the belief that the extent of hemoconcentration is related to the severity of the pathologic changes. It is possible that the supposedly secondary

67. Fender, F. A.: Lymphatic Pathology in Relation to the "Toxin" of Burns, *Surg., Gynec. & Obst.* 67:612-620 (Nov.) 1933.

68. Bardeen, C. R.: A Review of the Pathology of Superficial Burns with a Contribution to Our Knowledge of the Pathological Changes in the Organs in Cases of Rapidly Fatal Burns, *Johns Hopkins Hosp. Rep.* 7:137, 1898.

69. Donahue, J. K., and Parkins, W. M.: Lipoid and Hemorrhagic Changes in Adrenal Cortex Following Traumatic Shock, *Proc. Soc. Exper. Biol. & Med.* 32: 1249-1253, 1935.



changes in the adrenal glands may account for part of the irreversibility of the shock present in various clinical conditions.

Rewbridge<sup>70</sup> showed that the presence of the pancreas is necessary for the development of fat necrosis in peritonitis resulting from bile or bile salts.

GROUP 8.—*Toxicity of Bile and Bile Salts.*—Previous workers<sup>71</sup> have studied the toxicity of bile and bile salts more thoroughly than the province of this paper would permit, but certain tests were made to determine approximately the toxicity of the particular preparation of bile salts used. Four unanesthetized animals were given painless intravenous injections of a 10 per cent solution of bile salts. Two other animals were given injections intravenously under barbital anesthesia, and determinations of the blood pressure were made.

In experiment YY the animal received a total of 8 cc. of a 10 per cent solution of bile salts per kilogram of body weight divided into three equal doses at intervals of fifteen minutes. Death occurred two minutes after the last injection. Necropsy gave negative results, and the percentage of hemoglobin remained constant. In experiment ZZ death resulted three hours after the administration of 5 cc. per kilogram of body weight. Necropsy gave negative results and there were some hemoglobin concentration and slight decrease in the hematocrit reading. In experiment WW death resulted four and one-half hours after the injection of 5 cc., and in experiment XX there was recovery (still alive after three days) after the injection of a similar amount. The results in experiments AAA and BBB are shown in chart 4. In neither of these animals was there any blood concentration, as evidenced by the percentage of hemoglobin and the hematocrit readings. The animal in experiment AAA died following the administration of 4.3 cc. of a 10 per cent solution of bile salts per kilogram of body weight. In experiment BBB the animal was given a similar amount, as shown in the tracing, followed by an additional 1.2 cc. per kilogram of body weight immediately after the end of the recorded tracing, and was then bled to death. The volume of bleeding was determined at a time when the blood pressure was 60 mm. of mercury, being 225 cc., or 3.2 per cent of the body weight, which is distinctly above the average for secondary shock. The percentage of hemoglobin and the hematocrit readings in these two experiments were, respectively: AAA, control 115 and 57, in two hours, 96 and 49; BBB, control 94 and 44, in two hours 92 and 41, in eleven hours 96 and 42. These experiments indicate that about half or more of the animals die from the administration of 5 cc. of a 10 per cent solution of bile salts per kilogram of body weight. But

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70. Rewbridge, A. G.: An Experimental Study of Fat Necrosis in Bile Peritonitis, *Proc. Soc. Exper. Biol. & Med.* 28:128-129, 1930.

71. Brand.<sup>28</sup> Horrall.<sup>46</sup> Still.<sup>47</sup>

the absence of blood concentration, the nearly normal bleeding volume despite a low blood pressure and the absence of hemorrhagic changes in the adrenal glands, the mesenteric glands, etc., all are different from the effects of biliary peritonitis.

GROUP 9.—*Toxicity of Peritoneal Exudates.*—Bile peritonitis was produced in three animals by defundation of the gallbladder and ligation of the common duct, in two animals by the intraperitoneal injection of sterile whole gallbladder bile and in four additional animals by the intraperitoneal injection of a 10 per cent solution of bile salts. After an interval of from eighteen to ninety-six hours in the different animals, the contents of the peritoneal cavity were aspirated, and the peritoneal fluid was tested for effect on blood pressure of normal dogs under barbital anesthesia and of rabbits under ethyl carbamate anesthesia. In the tenth animal in this group, biliary peritonitis was produced by the intraperitoneal injection of bile salts, and after the changes in the blood concentration indicated that considerable reaction had set in the contents of the peritoneal cavity were aspirated, and the peritoneal exudate was immediately reinjected intravenously into the same animal.

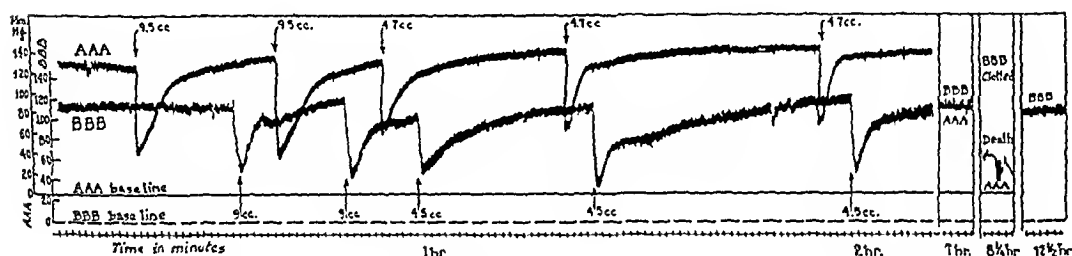


Chart 4.—Tracing showing the course of the blood pressure in two dogs given repeated small doses of bile salts intravenously. Dog AAA (weight 7.5 Kg.) died eight and one-fourth hours after the start of the experiment and received a total of 4.4 cc. of a 10 per cent solution of bile salts per kilogram of body weight. Dog. BBB (weight 7 Kg.) received an additional 9 cc. one hour after the end of the recorded tracing, and then was killed by bleeding. This dog received a total of 5.8 cc. of a 10 per cent solution of bile salts per kilogram of body weight.

In eight of the nine instances in which the peritoneal exudate was injected intravenously into other animals, there was no change in the blood pressure of the recipient animal. This is despite the finding of various organisms, including *Clostridium*, *B. coli*, *Staphylococcus* and *Streptococcus haemolyticus* in the exudate. All but one of these exudates were aspirated ante mortem, the other being obtained four hours post mortem. One of the exudates from a dog with peritonitis produced by the injection of bile salts gave a marked immediate fall in the blood pressure of the recipient dog. This exudate, however, was obtained eight hours post mortem and contained a heavy growth of *B. coli*, which organism has been shown by Harmon and Harkins<sup>66</sup> to have a vaso-depressor effect. The one animal which received its own entire peritoneal exudate followed the same course as other animals suffering a

similar type of peritonitis. It did not seem to be harmed and if anything was temporarily improved (discussed under "Attempts at Treatment"). In conclusion, it may be said that the peritoneal exudate produced by bile peritonitis has little effect either on other animals or on the same animal when injected intravenously if obtained before postmortem decomposition has set in.

GROUP 10.—*Attempts at Treatment.*—Thirty-five animals were used in this group of experiments. Sixteen animals received no treatment, and the remaining nineteen received various types of treatment. Bile peritonitis was produced in animals anesthetized with barbital or morphine and ether, aseptic technic being used in the usual manner with intraperitoneal injection of whole gallbladder bile or bile salt solution. The animals were then observed at frequent intervals by following the course of the percentage of hemoglobin and the hematocrit reading, and in two instances the blood pressure as well until the readings showed a serious condition to exist. Then any treatments were performed. The treatments included a combination of the following methods: simple aspiration of the peritoneal cavity either with or without additional washing out with sterile physiologic solution of sodium chloride, reinjection of the peritoneal exudate intravenously, transfusion of whole blood and intravenous injection of blood plasma. All treatments were performed with complete surgical aseptic technic. When whole blood was used, compatibility tests were performed between cells and serum of the donor and the recipient.

Of the thirty-five animals, only four lived more than seventy-two hours. Two of these were treated by simple aspiration of the peritoneal cavity, while one received in addition blood plasma and another whole blood intravenously. A summary of the results follows:

1. Bile peritonitis was produced by intraperitoneal injection of 2.5 cc. of 10 per cent solution of bile salts per kilogram of body weight. One untreated dog died in two days; one dog treated by aspiration and intravenous injection of peritoneal contents died (see group 9).

2. Bile peritonitis was produced by the intraperitoneal injection of 5 cc. of a 10 per cent solution of bile salts per kilogram of body weight. Seven untreated dogs died; of four treated by aspiration only, one recovered and three died. Two treated by aspiration and intravenous whole blood died and two treated with whole blood alone died.

3. Bile peritonitis was produced by the intraperitoneal injection of 7.5 cc. of a 10 per cent solution of bile salts per kilogram of body weight. Two untreated dogs died.

4. Bile peritonitis was produced by the intraperitoneal injection of 2 cc. of whole bile per kilogram of body weight. Three untreated dogs died and one treated by aspiration died.

5. Bile peritonitis was produced by the intraperitoneal injection of 4 cc. of whole bile per kilogram of body weight. Two untreated dogs died and one treated by aspiration and blood transfusion died.

6. Bile peritonitis was produced by the intraperitoneal injection of 5 cc. of whole bile per kilogram of body weight. One untreated dog died, and one treated by aspiration recovered. Of two treated by aspiration and blood transfusion, one died and one recovered.

7. Bile peritonitis was produced by ligation of the common duct and defundation of gallbladder. Two untreated dogs died, and three dogs treated by aspiration died.

Chart 5 shows the fall in blood pressure with a rise after blood transfusion in experiment NN. Although the total amount of peritoneal exudate found in this dog was less than the volume of blood administered intravenously, the blood pressure ultimately fell again and death ensued. At the same time there was a further concentration of the blood. In this experiment the amount of peritoneal exudate totaled 425 cc., 210 cc. being obtained at aspiration before giving the

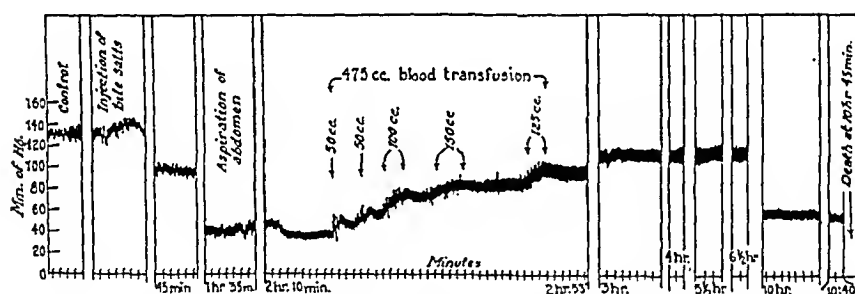


Chart 5.—Tracing showing ineffective blood transfusion in a dog (weight 14.5 Kg.) with bile peritonitis produced by the injection intraperitoneally of 72 cc. of a 10 per cent solution of bile salts. There was a decrease in the blood pressure after the institution of the peritonitis, with temporary recovery after the transfusion of 475 cc. of compatible blood, but ultimate collapse and death.

blood transfusion and 215 cc. at necropsy. Chart 6 shows a similar blood pressure curve in experiment MM, with fall in blood pressure, temporary recovery after transfusion and ultimate collapse and death. It is seen that the course of increasing blood concentration was temporarily arrested by the transfusion but ultimately became more marked. In other experiments in which the animals were given intravenous infusion of blood plasma, the hematocrit readings and the percentages of hemoglobin would return to near normal after the injection, but ultimately the blood would again concentrate.

GROUP 11.—*Effect of Bile and Bile Salts Injected Subcutaneously.*—Animals were given injections aseptically with bile or bile salts into the axilla and groin of one side after the midlines were marked carefully with india ink. After death the animals were bisected by Blalock's method.<sup>7</sup> Chemical analysis of the edema fluid

found near the site of injection was made. Cultures were taken from the edematous subcutaneous tissue and muscle after opening the skin aseptically with a thermocautery.

The results obtained in this group of experiments are to be reported in detail elsewhere. The average excess in weight of the side on which injection was made over the normal side was 3.5 per cent of the body weight. The fluid closely resembled blood plasma in its protein content. This high protein content indicates that the bile acts as an irritant rather than merely as an osmotic agent, attracting only water from the blood stream. Anaerobic cultures of the tissues were sterile in several instances despite the death of the animal. These results indicate that bile or bile salts can produce an irritative action sufficient to cause death by exudation of plasma-like fluid when placed elsewhere than in the peritoneal

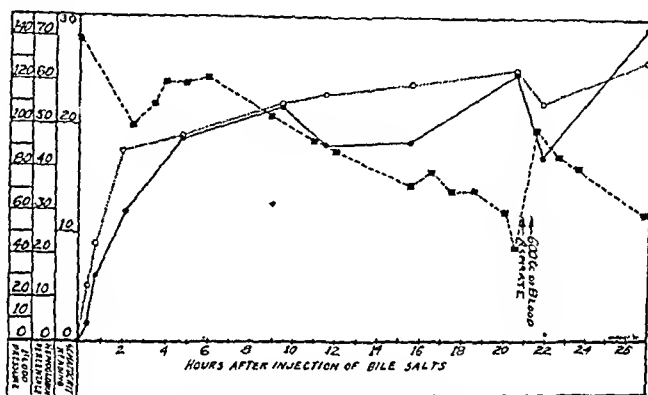


Chart 6.—Curves showing the results of ineffective blood transfusion in a dog (weight 20 Kg.) with bile peritonitis. The decrease in blood pressure, temporary recovery after transfusion and ultimate collapse are shown. The blood pressure is indicated by the broken line; the hematocrit readings, by the dotted line, and the percentage of hemoglobin, by the solid line. The animal died shortly after the last reading. The gradually increasing blood concentration is shown by parallel behavior of the lines representing the hematocrit readings and the hemoglobin percentages. This concentration is temporarily arrested by the transfusion, but later becomes more marked just before death.

cavity. Horrall<sup>46</sup> and Horrall and Carlson<sup>29</sup> noted edema following the subcutaneous injection of a solution of bile salts but did not report its amount. Andrews, Rewbridge and Hrdina<sup>54</sup> made similar observations and in addition showed that bile salts placed in the pleural cavity produced a pleural exudate.

GROUP 12.—*Report of a Case of Bile and Colon Bacillus Peritonitis, Probably the Result of Perforation of the Biliary Tract.*<sup>72</sup>—G. H.; a plumber, married, aged 56, entered the University of Chicago Clinics on Nov. 8, 1934, with the complaint

72. Dr. Lester Dragstedt granted us permission to report this case.

of abdominal pain of two days' duration. Previous to the present illness he had been quite well and had never had abdominal pain, any form of indigestion or symptoms of disease of the gallbladder and had never been jaundiced. The present illness began two days before admission to the hospital, when he began to have some mild epigastric distress. The day before admission he was seized with a sudden, severe epigastric pain. The pain was entirely localized to the middle of the abdomen and did not radiate to the back, shoulders or arms. He vomited with the pain and since that time continued to vomit small quantities of "bile-stained" fluid. Because of the persistence of the pain, the local doctor made a diagnosis of ruptured peptic ulcer and referred him to the clinics.

On admission the temperature was 101.8 F. (oral), the pulse rate 160, the respiratory rate 40, and the blood pressure 110 systolic and 76 diastolic. The patient was suffering great pain in the abdomen, exaggerated by breathing, and during the examination he vomited about 40 cc. of greenish fluid. He passed no stools during his stay in the hospital. The first examiner thought that he found consolidation in the lower lobe of the right lung and stated that there was no rigidity but extreme generalized tenderness over the abdomen. There was an icteric tint to the scleras. The patient was believed to have lobar pneumonia of the lower lobe of the right lung and was treated accordingly. Because of the persistence of pain in the abdomen, he was seen by Dr. L. R. Dragstedt eight hours after admission. At that time it was difficult to be certain as to icterus of the scleras because of artificial illumination. There was no evidence of consolidation of the lower lobe of the right lung, and the abdomen revealed not only generalized tenderness but boardlike rigidity. The pulse was imperceptible; the skin was cold and clammy, and the temperature was 100.4 F. A diagnosis of ruptured viscus and generalized peritonitis was made, and the patient was immediately prepared for exploratory laparotomy. Because of the condition of shock, a transfusion of 500 cc. of citrated blood with 250 cc. of physiologic solution of sodium chloride was given intravenously before operation, which was done at 8 p. m. on November 8.

Operation was performed by Dr. L. R. Dragstedt with the patient under local anesthesia, later supplemented by ethylene and oxygen. The abdomen was opened through a paramedian incision in the right upper quadrant. As soon as the peritoneum was opened, a considerable amount of yellow exudate welled into the wound. About 200 cc. of this material was removed, a large amount coming from the region of the gallbladder and a large amount from the right side of the pelvis. The intestines were covered everywhere with exudate, and all the tissues were very edematous. The gallbladder was not visualized because of adhesions, and no perforation of other viscera was seen. The abdomen was closed with drainage.

The patient's blood pressure, which had been 120 systolic and 80 diastolic at the start of the operation, became unreadable before the end. The pulse rate averaged 140, and forty-five minutes after the end of the operation the blood pressure was 96 systolic and 80 diastolic. Caffeine with sodium benzoate, coffee by rectum and hypodermoclysis of 1,500 cc. of physiologic solution of sodium chloride were given, and a Wangenstein suction apparatus was inserted. At 11:20 p. m. the blood pressure had risen to 110 systolic and 84 diastolic, the pulse rate was 144 and the respiratory rate was 64. An hour later the blood pressure had fallen slightly, and the temperature was 104.2 F. (axillary). At 1:45 a. m. on November 9, the blood pressure was 100 systolic and 72 diastolic, and thereafter the radial pulse and blood pressure were unreadable. The patient died at 2:45 p. m.

The leukocyte count was 8,000 on three successive readings on the day of admission; the hemoglobin content was 92 per cent, and the red cells numbered 5,100,000, on admission. Roentgen examination revealed elevation of the right half of the

diaphragm. The Wassermann reaction was negative, and the Kahn reaction weakly positive. The electrocardiographic examination revealed only sinus tachycardia. Culture of the peritoneal exudate revealed *B. coli*. Anaerobic cultures were negative (swab technic). Chemical analysis of the peritoneal fluid showed bile (strongly positive reaction), nonprotein nitrogen 80 mg. per hundred cubic centimeters, protein 5.55 Gm., sugar 200 mg., sodium chloride 502 mg. and globulin 120 mg.; the albumin-globulin ratio was 31.

The gallbladder was not visualized during the operation, and from the clinical standpoint it is difficult to be sure of the relation of this case to bile peritonitis. Permission for autopsy was not obtained. The results of the laboratory examinations agree in many respects with observations on experimental bile peritonitis, such as the fall in blood pressure and the chemical composition of the peritoneal fluid. Although only 200 cc. of fluid was recovered from the abdomen and measured, considerable more fluid escaped on the sheets and dressings when the peritoneal cavity was opened and more was left behind. Even after making allowance for this, it is not certain that the amount of fluid pres-

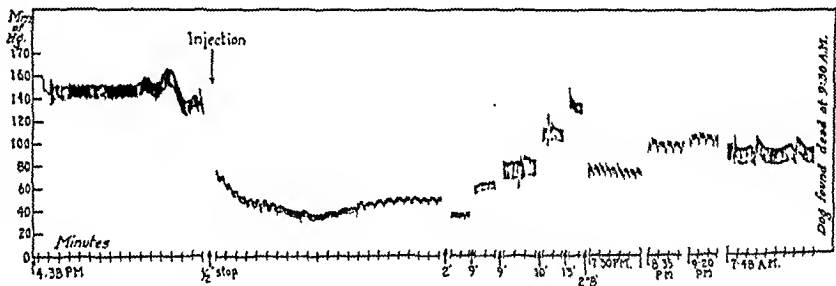


Chart 7.—Tracing showing the effect of the injection of peritoneal exudate (83 cc.) from a man with bile peritonitis on the blood pressure of a dog (weight, 16 Kg.). The tracing was started at 4:38 p. m. one afternoon and ended the next morning.

ent was sufficient to cause death in this patient. Perforation of a gangrenous gallbladder may have been present. Anaerobic cultures of the peritoneal fluid remained sterile; aerobic cultures showed only *B. coli*. The effects of intravenous injection of peritoneal fluid into a dog are shown in chart 7. There was some accompanying slight blood concentration. The profound fall in blood pressure may be explained by the presence of *B. coli*, as Harmon and Harkins<sup>68</sup> have shown that this organism is the chief vasodepressive bacterial factor present in peritonitis.

#### COMMENT

Although previous workers have been about equally divided in crediting toxic action and anaerobic bacterial invasion as being the chief lethal factors in bile peritonitis, the present work indicates that there must be an additional factor. Chief objections to the theory that the

toxic action of bile or its salts is the sole factor are the lack of absorption into the blood stream above the concentrations found in mild degrees of jaundice and the fact that bile peritonitis will be fatal after the intraperitoneal injection of a smaller amount of bile than the minimum lethal intravenous dose. Furthermore, injection of the peritoneal exudate intravenously into other dogs was found to be accompanied by only slight changes. The chief objections to the bacterial theory will be presented in the second paper in this series; suffice it to say here that any organism that is not found frequently except in the terminal stages of a condition or at postmortem examination, and then not constantly, can hardly be credited with the sole etiologic rôle in that condition. For an organism to be imputed with being a major factor it is necessary that it be found in the early stages of a condition and that its growth to some extent parallel the progress of the condition. Although these requirements as stated in the past few sentences are far from being as strict as Koch's postulates, the anaerobic organisms do not fulfil them in bile peritonitis.

In a search, therefore, for a further explanation of the rapid death in bile peritonitis, a correlation was made between certain findings in bile peritonitis and recent advances in the study of experimental shock. The intraperitoneal injection of bile or bile salts was found to produce a profound lowering of blood pressure several hours after injection, with a marked decrease in the bleeding volume. Accompanying this fall in blood pressure was a marked concentration of the blood. This marked concentration seemed to indicate a preservation of the volume of the erythron and a loss of blood plasma. As the peritonitis developed, there was an enormous effusion of blood-stained fluid into the peritoneal cavity. This fluid clotted spontaneously, and chemical analysis showed it to be similar to blood plasma in its sugar, chloride, nonprotein nitrogen and protein contents. It usually contained more albumin and less globulin than did the blood plasma. Accompanying the development of the peritonitis there was an increase in the nonprotein nitrogen (as to how much of this content might be due to absorbed bile salts no experiments were made) and a decrease in the chloride content and a relative proportion of the albumin in the blood plasma. This indicated that the blood plasma leaked markedly into the peritoneal cavity but that, as usually happens when there is a loss of protein in the plasma, the albumin escaped more easily than the globulin.

Experiments indicated that in addition to the plasma-like fluid lost into the peritoneal cavity there was some loss by hemorrhage and edema in the exposed visceral and parietal peritoneal membranes and by hemorrhage into the lumen of the bowel, with occasionally bloody diarrhea. Pathologic examination revealed hemorrhagic and some necrotic changes in the abdominal organs, especially in the intestines, adrenal glands and mesenteric lymph glands.



Confirmatory evidence for the importance of these shocklike changes in bile peritonitis was afforded by the observation that the injection of bile or bile salts subcutaneously was accompanied by a tremendous local effusion of plasma-like fluid in amounts sufficient to account for the death of the animal. All of these facts indicate that the loss of blood plasma-like fluid into the peritoneal cavity and surrounding tissues with resultant secondary shock is a lethal factor of importance sufficiently great to warrant its recognition.

It must be stated, however, that surgical shock may not be the only lethal factor in bile peritonitis. The toxic action of the bile and secondary growth of anaerobic organisms may hasten death in an animal already in shock. Furthermore, the loss of plasma-like fluid in certain of the experiments has not always been as much as would be necessary to account for death from that cause alone.

The experiments on the bleeding volume showed that the average volume in four animals with bile peritonitis was 1.8 per cent of the body weight, which is 2.3 per cent less than the control value of 4.1 per cent found in another series of animals. Of this 2.3 per cent, 1.8 per cent can be accounted for by the peritoneal exudate and possibly 0.2 per cent by leakage of blood and plasma into the abdominal viscera. These interesting calculations leave little additional decrease in the bleeding volume to be accounted for. The slight difference might be attributed to a general increase in the permeability of the vascular system with generalized leakage of plasma if it were not that the experimental error of the measurements involved is too great to allow such fine distinctions to be drawn. It is quite probable, however, that the loss of plasma is greater than the leakage into the peritoneal cavity alone and possible that the factor of surgical shock in bile peritonitis is more important than even the amount of peritoneal fluid would indicate.

#### SUMMARY AND CONCLUSIONS

1. The two factors hitherto considered most frequently in the literature as important in the production of death in bile peritonitis are the toxic action of absorbed bile and the effects of anaerobic bacteria.

2. In the present article experimental data are presented to advance the view that the changes commonly found accompanying so-called secondary surgical shock are an important lethal factor in bile peritonitis.

3. The mechanism of production of this surgical shock includes an escape of considerable amounts of plasma-like fluid into the peritoneal cavity with associated hemoconcentration, fall in blood pressure and decrease in the bleeding volume.

4. The condition of surgical shock is not considered to be the entire explanation of death in experimental animals. However, the shock is of such a degree as to make the animal an easy victim of bacterial or toxic factors that would be less harmful to a normal animal.

# HISTOPATHOLOGIC STUDY IN A CASE OF PERTHES' DISEASE OF TRAUMATIC ORIGIN

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The clinical manifestations and etiology of Perthes' disease have been treated in a great number of articles in the English and foreign literature. There is still no agreement as to the etiology. Vascular disturbance of the upper epiphysis of the femur and inflammatory and metabolic changes have been discussed, besides the purely traumatic factor. It seems, however, that trauma as an etiologic factor is coming more and more into the foreground.

The pathologico-anatomic features of this lesion have not aroused as much interest as the clinical picture, owing to the difficulty of obtaining material. There are only a few reports on human material, most of the pathologic work being based on experiments on animals. Therefore, it will be of interest to report a case in which there was a definite history of trauma with a lesion of the upper epiphysis of the femur which corresponded in its clinical, roentgenologic and pathologic manifestations to that of Perthes' disease.

## REPORT OF A CASE

### CLINICAL DATA

*History.*—The patient, a white boy of 14 years, was first seen in November 1934, with the chief complaint of pain and stiffness in the left hip joint. Three years prior to this time he had been injured, when a horse on which he was riding stumbled and fell, pinning the patient's left hip to the ground. The pain immediately after injury was not severe, so the boy received no treatment but continued to walk with a slight limp, which persisted for two months. During the next two years he was apparently free from symptoms. Pain then recurred, gradually becoming more severe, especially after overuse of the joint, and at the time of his admission to the clinic a constant dull ache was present in the hip.

The past history was essentially irrelevant. The patient's development had been normal, and his general health was good. There was no familial incidence of tuberculosis, syphilis, diabetes or disease of the endocrine glands.

*Physical Examination.*—The patient was rather tall, fairly well developed and apparently normal. There were no external signs of rickets.

*Left Hip:* The left hip joint at rest was in flexion of 30 degrees, abduction of 25 degrees and slight outward rotation. From this position there was a possibility of active flexion of 70 degrees, adduction of 25 degrees and internal rotation

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of 5 degrees; abduction and external rotation were absent. There was shortening of  $\frac{1}{4}$  inch (0.6 cm.). Marked pain was produced by pressure in the left groin over the neck of the femur and by forced passive movements of the hip joint.

*Roentgenographic Examination.*—The roentgenogram of the proximal end of the left femur (fig. 1) showed a lesion similar to that of Perthes' disease. The changes consisted of compression of the epiphysis, the greater part of which appeared as an irregular, dense shadow. There was an area of resorption of bone between the medial pole and the central portion of the epiphysis, below the insertion of the ligamentum teres. Corresponding to this lesion, the juxta-epiphyseal portion of the neck of the femur also showed an area of more circumscribed osteoporosis. Opposite the outer edge of the roof of the acetabulum there was a defect in the flattened head of the epiphysis of the femur, which separated the



Fig. 1.—Roentgenogram of the left hip joint, showing compression of the head of the femur with necrosis of the epiphysis. There is a focus of resorption close to the insertion of the ligamentum teres and opposite the outer edge of the roof of the acetabulum, with preservation of the joint space.

lateral pole of the head of the femur from the central portion. The lateral pole was markedly displaced over the superior surface of the neck, so that it almost touched the inner surface of the greater trochanter. There were practically no changes in the acetabulum except for osteoporosis. The joint space was of about normal width, and the joint surface of the femur was fairly smooth.

*Operation.*—Because of the deformity, pain and stiffness of the joint, subtrochanteric osteotomy or arthroplasty of the hip joint was considered. Arthroplasty was performed, as it seemed to be the more promising procedure. Through a Smith-Peterson incision the left hip joint was exposed. The musculature over the hip joint was observed to be in excellent condition. The capsule was opened and the head dislocated. It was misshaped, and its diameter was considerably

enlarged, owing to the flattening of the head, with the formation of marginal exostoses. There was relatively well preserved joint cartilage, except for a wide area of erosion around the insertion of the ligamentum teres. The ligamentum teres itself was covered by thickened synovial tissue, which was hyperemic. The ligamentum teres was cut far down at its origin in the acetabulum. The synovial tissue on the inside of the joint capsule was also markedly hypertrophic and hyperemic and was partially removed from the neck. The head of the femur was chiseled from the neck as close as possible to the epiphyseal plate, which remained in complete connection with the head. The operation which followed was a typical arthroplasty, with the removal of a fascial flap from the thigh and suture to the trimmed neck. Nothing was done to the acetabulum. The patient was

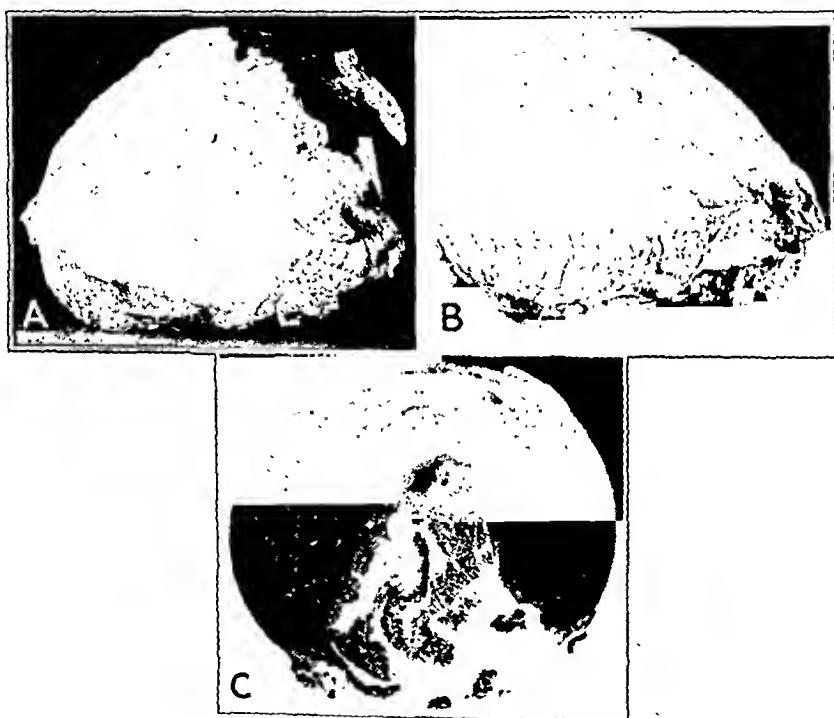


Fig. 2.—Photograph showing three views of the head of the femur: *A*, lateral; *B*, from behind, and *C*, from above. The joint cartilage is uneven, with extensive erosion over the medial portion of the head. The ligamentum teres is markedly thickened and flattened over the eroded area. The margins of the joint are irregular.

placed in a double hip spica cast, and the left leg was kept in abduction of 25 degrees, full extension and some internal rotation. Roentgenograms taken after operation showed that the neck was reshaped and conelike and was well centered in the acetabulum with the leg in a position of abduction.

*Postoperative Course.*—Ten days after operation the cast was removed, and the left leg was placed in traction. Passive movement in the hip joint immediately after removal of the cast was as painless on flexion of from 18 to 145 degrees and abduction of 25 degrees and outward rotation of 10 degrees. Hardly any inward

rotation was present. Physical therapy, with use of passive and active motion, was started gradually. Six weeks afterward the patient was allowed to get up on crutches, without weight bearing, and was discharged from the clinic. Five months after operation the roentgenogram of the left hip joint showed essentially the same condition as did the film taken immediately after operation. Flexion and extension, as well as abduction and adduction, were free; there was some degree of external rotation but little internal rotation. The patient was able to bear weight on his left leg without pain.

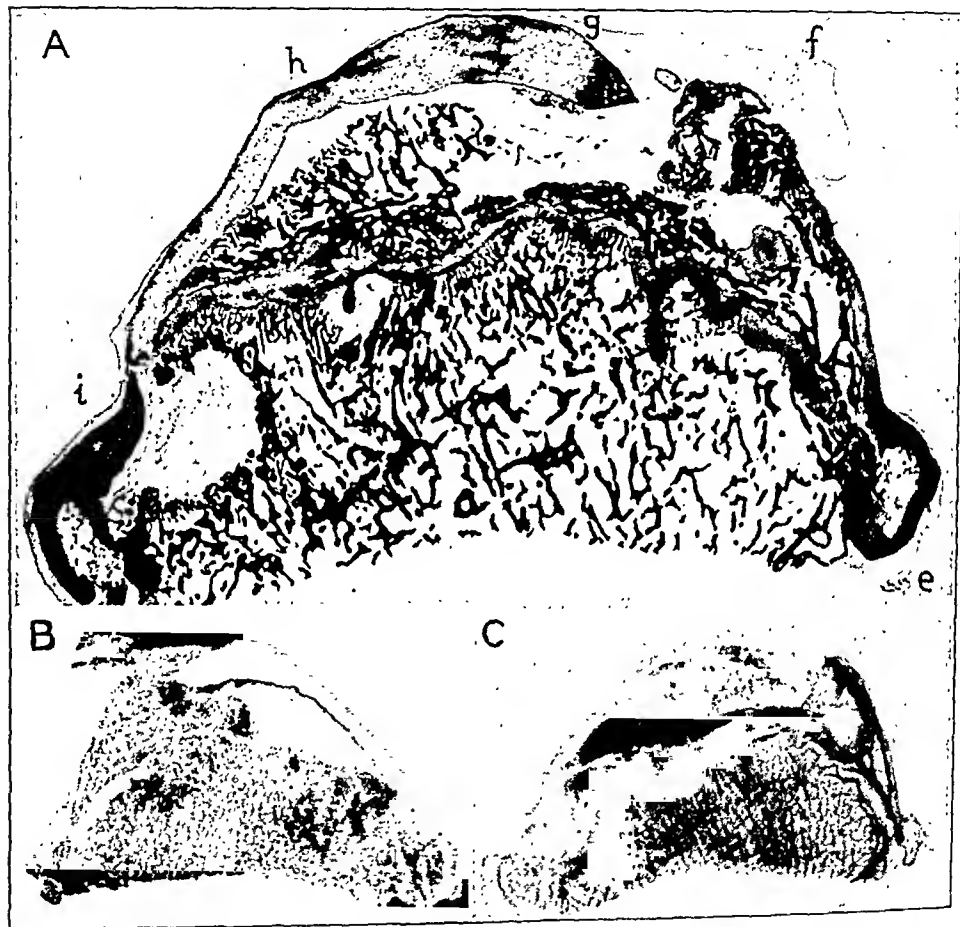


Fig. 3.—Photograph (B) and roentgenogram (C) of a section of the head of the femur, with a drawing of the corresponding microscopic section (A). The medial portion of the epiphysis is regenerated, with thin joint cartilage and a small joint body (e). The ligamentum teres (f) shows the formation of a pannus (g) over the joint cartilage. There are a subchondral fracture space, with a necrotic rest of the epiphysis (h) and a deep defect in the neck of the femur (i), opposite the outer edge of the roof of the acetabulum.

#### PATHOLOGIC EXAMINATION

**MACROSCOPIC OBSERVATIONS.**—In addition to the findings already recorded in the history of the operation, the following observations were made: The lateral part of the superior portion of the head of the femur (fig. 2) was flattened, and the

medial portion was steep, so that the head from the front appeared pyramidal. The joint cartilage was uneven, with a few small, irregular areas over the apex where small defects in the cartilaginous cover had healed with the formation of a fibrous



Fig. 4.—Photographs (A) and roentgenograms (B) of four sections through the head of the femur a section of which is shown in figure 3, demonstrating the marked irregularity of the epiphysis, with fragmentation at the insertion of the ligamentum teres. The subchondral fracture space and the waviness of the epiphyseal plate are evident.

pannus. A large defect was present medial to the ligamentum teres. The defect extended from the fovea to the margin of the joint surface and was covered by fibrous tissue and fibrous cartilage. Through a frontal plane the head was cut in an anterior and a posterior half. The cut surface showed marked reduction of the epiphyseal nucleus, which could be differentiated into a medial and a lateral portion. The medial portion was covered by fibrous tissue and fibrous cartilage only, which extended laterally beyond the fovea capitis. The bony tissue of this portion was not uniform; and its fibrous marrow included several irregular islands



Fig. 5.—Photomicrograph of the necrotic portion of the capital epiphysis of the femur, covered above by joint cartilage, showing poor nuclear stain in the deep layers. The bony trabeculae possess normal strength and structure. The bone marrow spaces are filled with amorphous calcified detritic material, deriving from the near-by subchondral fracture space.

of cartilage. The lateral portion was stained sulfur yellow and was separated from the medial darker portion by a sharp borderline. This portion represented the condition of aseptic necrosis. A line of fracture ran through the necrotic area just below the joint cartilage, which was relatively well preserved over this area. The epiphyseal plate was apparently without pathologic change. Along its entire length it showed a bluish line on the diaphyseal side, corresponding to the region of cartilaginous proliferation.

**MICROSCOPIC OBSERVATIONS.**—For purposes of detailed histologic examination the two halves of the head of the femur were further sectioned into several smaller portions (figs. 3 and 4). Each section was studied thoroughly, and the observations were recorded and summarized so as to give a representative, composite picture of the process of aseptic necrosis as it occurred in this case. All the changes in the head of the femur as seen in these sections may be explained as follows: First, the original trauma led to compression of the spongy bone and to subsequent aseptic necrosis. Fibrous tissue invaded the involved areas in an attempt to resorb the dead bone. This resorption led to diminished resistance of the epiphyseal nucleus. Under certain mechanic stresses, such as weight bearing, this weakening of the bony structure in turn caused secondary traumatic changes in the bony tissue as well as in the joint cartilage, epiphyseal plate and synovial capsule. Since the bony changes were of primary importance, they will be discussed first. The secondary changes in the joint cartilage, capsule and epiphyseal plate are also presented in this paper.

*Epiphysis.*—Necrotic Bone: Aseptic necrosis of the bony nucleus (fig. 5) as it appeared at the time of trauma could be seen only in the central portion. This relatively small central area consisted of dense spongy bone. The density of the bony tissue was not due to sclerosis, as the bony trabeculae in this area were of normal thickness and did not show any signs of bone apposition. Only on the epiphyseal side of the epiphyseal plate could a continuous and dense bony lamella be seen. This bony lamella, like the other necrotic bony trabeculae, showed absence of nuclear staining of the bone cells. However, in a few places close to the cartilage a few bone cells could be seen with good nuclear stain, which makes it likely that these cells had escaped necrosis. As all the other bone cells were without nuclear stain, it must be assumed that close to the epiphyseal plate bony trabeculae derive their nutrition by diffusion or osmosis of nutritive substances through the cartilaginous epiphyseal plate.

Necrotic Bone Marrow: Like the bony trabeculae the bone marrow in this area showed complete necrosis (fig. 5). As a rule, it was impossible to make out any histologic detail in the structure of the necrotic bone marrow. All the marrow spaces were filled with amorphous detritic material and irregular bony fragments, derived from a fracture space which ran through the subchondral region.

Subchondral fracture (figs. 6 and 7). It is questionable whether this subchondral fracture, which typically ran parallel to the joint surface, was caused by the compression fracture of the epiphysis alone or whether it developed later, after resorption and reorganization of necrotic bone had already taken place. Both possibilities must be considered. However, in such an advanced stage as that in the present case it is impossible to make a definite statement as to whether the fracture line was primary or secondary to the aseptic necrosis. This subchondral fracture space, owing to the constant friction between the joint cartilage and the subchondral necrotic spongy bone, contained detritic material and fibrin as well as larger pieces of bone in connection with calcified cartilage, representing small sequestrums of the subchondral hard substances. At one side the subchondral fracture space forked into two branches, which separated a rather large wedge-shaped piece of necrotic spongy bone from the main necrotic portion of the epiphysis. The constant friction led to gradual disappearance of the spongy bone of the epiphysis and, at the same time, to accumulation of detritus in the fracture space. With every increase in pressure particles of calcium-containing material became gradually massaged into the deeper marrow spaces until nearly all the marrow spaces were filled with detritic material. The marrow spaces close to the fracture space adjoined bony trabeculae, which showed splitting of the bony



lamellae and bending and torsion fractures in many instances. There the marrow spaces were densely filled with the same type of necrotic material as was noted in the subchondral fracture space; the material was also present in somewhat looser form in the marrow spaces close to the epiphyseal plate. In other places, however, some of the marrow spaces close to the epiphyseal plate still showed definite structure of necrotic fatty bone marrow. This picture was of great interest because it showed that the bone marrow at the time when aseptic necrosis of the head of the femur occurred was essentially fatty bone marrow. Later, after the



Fig. 6.—Photomicrograph showing fibrous tissue extending like a pannus from the fovea capitis over the joint cartilage, which becomes resorbed along a sharp lacunar outline. There is incomplete resorption, with preservation of collagenous fibers, in the end of the joint cartilage. The fibrous tissue enters the epiphysis and extends, with organization, toward the subchondral fracture space, which on one side is still walled off by a rest of subchondral bony tissue. There is complete loss of basophilia of the joint cartilage, but no sign of necrosis.

formation of detritus along the subchondral fracture space, the marrow spaces gradually became filled with the detritic material. The marrow spaces farther from the subchondral fracture space were the last to be filled with detritus, and

therefore they showed for some time the more or less normal structure of fatty bone marrow. Owing to this process the height of the epiphysis gradually became decreased. The roentgenographic shadow, however, became progressively darker and gave the impression of true osteosclerosis.

**Reorganization of the Epiphysis:** The process of reorganization of the necrotic part of the epiphysis consisted in extensive bone resorption and formation of new bone. These two processes were not simultaneous but apparently were separated by quite an interval.

**Resorption of necrotic bone.** The first process of reorganization was pure bone resorption, which started from different parts of the epiphysis. In this case

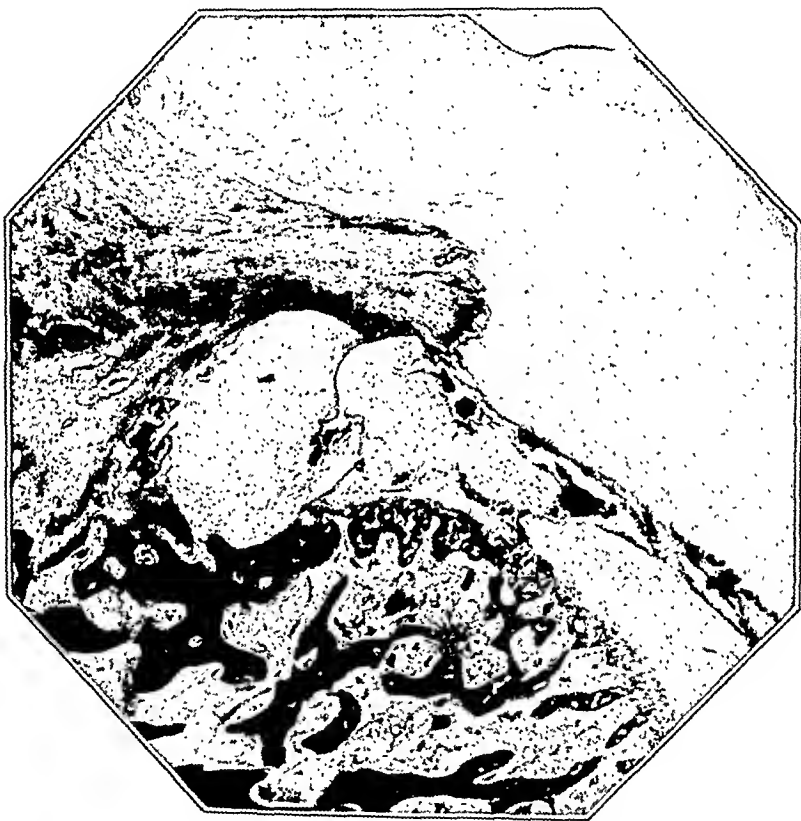


Fig. 7.—Photomicrograph showing fibrous tissue filling the defect between the joint cartilage and the metaphysis after removal of the necrotic bone in the epiphysis. The epiphyseal plate shows defect and traumatic interruption and is separated from the joint cartilage only by a thin layer of fibrous tissue or by the subchondral fracture space. There is a fibrous tissue pannus on the surface of the joint cartilage.

the fibrous granulation tissue showed two sites of origin. It developed first from the ligamentum teres (fig. 8) and second from the epiphyseal poles (fig. 7), where fibrous granulation tissue derived from the diaphyseal marrow spaces entered the necrotic epiphysis through fractures in the epiphyseal plate or along the nutritive cervical arteries. The fibrous tissue which derived from the ligamentum teres was so rich in vessels that in some places a picture resembling that of angioma

resulted. This fibrous tissue grew toward the necrotic bone marrow and spongy bone. The borderline between the invading fibrous tissue and the necrotic area sometimes could be seen as a relatively sharp line, along which a great number of multinuclear giant cells were present.

These cells were phagocytic elements, which resorbed the amorphous detritic material within the necrotic bone marrow as well as the necrotic bony trabeculae, which showed sharp lacunar outlines. In other places, however, more gradual invasion of fibrous tissue into the spaces of the necrotic bone marrow occurred, and the formation of fibrous tissue was preceded by invasion of a number of mononuclear cells, which advanced into the necrotic area for some distance. These cells were almost exclusively mobile fibrocytes, which could be seen within the necrotic area and possessed no collagenous fibers. Formation of fibers and multi-



Fig. 8.—Photomicrograph showing organizing fibrous tissue in the subchondral zone of the head of the femur, which is removing the necrotic fragments of the bony trabeculae and entering the subchondral fracture space, filled with coagulated fibrin. The joint cartilage shows good nuclear stain.

nuclear giant cells followed, and then granulation tissue could be seen, which included smaller areas of necrotic spongy bone and detritic material, surrounded by small granulomas with osteoclasts. These fibrocytes also had bone-resorbing properties, because often at the surface of the necrotic bony trabeculae, close to the living fibrous tissue, mononuclear cells could be seen in Howship's lacunae. Leukocytes and other forms of inflammatory exudative cells were absent.

From this reorganizing fibrous tissue new bone marrow developed in the epiphysis. This new bone marrow was hyperemic and edematous. Fat cells were more abundant in the peripheral portion, where the process was older and there were greater edema and lymphocytic infiltration close to the area of necrosis,

where the process was younger and resorption and reorganization were still more active. Besides lymphocytic infiltration a number of large protoplasmic cells, loaded with yellowish pigment granules, could be seen. These cells were evidently phagocytic histiocytes, which resorbed blood pigment after hemorrhage. In places where the process of reorganization was more advanced the bone marrow changed from fibrous to fatty bone marrow.

The process of reorganization at the margins was essentially the same as that at the fovea, which derived from the ligamentum teres. However, the process at the margins was more rapid, and led to earlier resorption of necrotic tissue than the process derived from the ligamentum teres.



Fig. 9.—Photomicrograph showing the epiphyseal plate, the diaphyseal side of which displays normal enchondral ossification. The epiphyseal side has marked irregularity of outline and structure and to the right is covered by a newly formed bony lamella, with hyperemic organizing fibrous tissue. To the left the old bony lamella shows signs of traumatization, with necrosis of the bony tissue and bone marrow. There are beginning invasion of the areas of interruption by fibrous tissue and fissures, filled with a fibrinoid substance, in the cartilaginous substance of the epiphyseal plate.

There was, in addition, a third site where resorption of the necrotic bony trabeculae of the epiphysis took place, but in a considerably less degree. This area was in the marrow spaces close to the epiphyseal plate (fig. 9), and became invaded by mononuclear cells of the fibrocytic type (derived from the epiphyseal plate), which led to some lacunar resorption of the necrotic bone.

To recapitulate: The loss of necrotic epiphyseal substance occurred in three ways: (1) the cellular resorption of necrotic bone and bone marrow by mononuclear and multinuclear cells at the margins of the organizing fibrous tissue; (2) the loss of substance by friction along the subchondral fracture space, forming a detritus which became massaged into the marrow spaces of the necrotic epiphysis, and (3) as will be explained later, the loss of this detritic material from the subchondral fracture space as it passed through fissures of the joint cartilage into the joint cavity.

New bone formation (figs. 8 and 10).—The second stage in the process of reorganization was the formation of new bone and bone marrow on the basis of the invading fibrous granulation tissue. Most of the new bone formed, rather peculiarly, along the epiphyseal side of the epiphyseal plate and the lower surface of the joint cartilage. Thus, there developed in the epiphysis a defect filled with



Fig. 10.—Photomicrograph showing regeneration of bone, in an attempt to fill the bony defect in the region of the fovea capitis. The young fibrous bone tissue has the appearance of endosteal osteophytes, with osteoid layers and osteoblasts.

fibrous tissue and surrounded below and medially by relatively dense bony tissue. This process of bone production was still active and could be observed in its earliest stages near the fovea capitis. There a relatively dense mass of bony tissue, like a tongue, extended along the inferior surface of the joint cartilage toward the insertion of the ligamentum teres. Its bony trabeculae were composed of primitive fibrous bone and lamellar bone tissue. The latter tissue was observed typically at the trabecular surface. This suggests that the bone was primarily of the primitive fibrous type, followed by osteoblastic bone apposition at the surface of the fibrous bone.

However, the new bone production appeared partly as a kind of callus formation, in which cartilaginous and bony tissue developed simultaneously on the basis

of fibrous tissue or cartilaginous tissue underwent enchondral ossification, with formation of irregular primitive spongiosa. This spongiosa was composed of trabeculae, showing many blue, often irregular lines of cement and apposition, indicating active bone formation. Where this tongue-like bony mass bordered on the fibrous tissue, filling the defect of the epiphysis under the fovea capitis, the new bone formation was arranged as radial spicules, with wide osteoid layers and incomplete calcification. This picture corresponded to the formation of periosteal and endosteal osteophytes. These new-formed bony trabeculae rapidly became transformed by osteoclastic resorption and osteoblastic bone apposition to more mature lamellar bone, with more static arrangement of the bony trabeculae. The density of the newly formed bone rapidly decreased in its older layers, owing to osteoclastic resorption, and the entire bone formation was gradually changed to porotic spongy bone, which was observed to fill the epiphyseal poles.

The question arose as to whether the aseptic necrosis caused by the compression of the head of the femur had involved the entire epiphysis or whether the marginal portions had escaped necrosis. The whole area of the medial as well as the lateral pole showed living bony tissue and living bone marrow. This living bony tissue must be considered to be of secondary development, following removal of the necrotic bone. This assumption was well borne out by observations in the region of the medial pole, the deformity of which was so marked that the bone must have undergone necrosis. The bony epiphysis in this area was of such negligible height that the joint cartilage was separated from the epiphyseal plate by two or three marrow spaces only. The process of reorganization must have started, therefore, in the epiphyseal poles, gradually proceeding toward the center of the epiphysis. It is of interest to note that the process of new bone formation was relatively slow in the restored areas. However, in the zone where bony tissue bordered on the reorganizing fibrous tissue there was relatively advanced bone sclerosis. This was true in the region of the fovea capitis as well as in the area between the lateral pole and the center.

The newly formed bone which lay along the epiphyseal side of the epiphyseal plate showed an interesting character. As the organizing fibrous tissue reached this side of the epiphyseal plate and removed the necrotic bony lamella, a new plate, primitive in form, was again apposed to the cartilaginous surface. This can also be interpreted as an attempt at restitution, which corresponds well with the continuous bony lamella on the epiphyseal side of a normal epiphyseal plate. The new bony lamella was of irregular structure and course and often still included portions of old necrotic bone. Some places in this area revealed new bone, which was formed on the surface of old necrotic bony trabeculae. In this way it is possible that the calcium content of the necrotic trabeculae was used to build new bone.

Cartilaginous islands (figs. 5 and 7). Islands of cartilage were observed frequently, varying in size from small cell groups to large masses of cartilaginous tissue, in different portions of the epiphysis as well as in the diaphysis, where they lay between the bony trabeculae. These islands resembled each other in the complexity of their relationship to the neighboring tissues. On one side the island might gradually blend into the fibrous tissue; on another it might show condensed collagenous fibers, resembling perichondrium, and on still another border preparatory calcification and irregular atypical enchondral ossification (usually lacking the zone of proliferation of cartilaginous cells) might be observed. In other places lacunar resorption by multinuclear chondroclasts occurred, as well as incomplete resorption by fibrous tissue. In some areas, however, there was gradual blending of cartilage into primitive fibrous bone. But since there was

no definite proof of such metaplasia, it is probably safer to assume that the connection of cartilage and bony tissue was local and not genetic; that is, cartilage and bone tissue had formed on a common fibrous tissue matrix.

Although the appearance of these cartilaginous islands and their relation to the adjacent tissue were similar, they differed as to origin. One group was of traumatic origin, due to proliferation of displaced fragments arising from the joint cartilage or the epiphyseal plate or to herniation of the cartilaginous tissue of the epiphyseal plate into the neighboring marrow spaces. These prolapses later might become separated from the epiphyseal plate and thus form isolated cartilaginous masses. A second group of islands was derived from callus formation in the fibrous granulation tissue. In a third group the appearance may be explained on the basis of static-mechanical irritation as follows: Owing to extensive resorption of necrotic spongy bone in a given area, the joint cartilage, which was deprived of solid support, deviated toward the epiphysis and exerted pressure on the fibrous tissue filling the defect. The central younger portion of this fibrous tissue was rich in vessels and therefore resembled a sponge; thus it easily resisted pressure. Increase of pressure merely led to expression of blood from the vessels and prevented refilling. By this mechanism fibrous tissue could easily escape damage from pressure. However, the older fibrous tissue at the periphery at that time was not rich in vessels, and where it glided over the bony tissue several islands of cartilaginous tissue developed, due to the mechanical irritation of the fibrous tissue. The investigations of Roux indicated that this kind of gliding motion represents a functional stimulus to the formation of cartilaginous from fibrous tissue. That the fibrous tissue is the basis of this cartilage was proved by the presence of blood vessels, which were included in this type of new primitive cartilage.

A relatively large island of cartilage lay close to the epiphyseal plate, where it showed distinct evidence of traumatization. Therefore, it is likely that this island also derived from the epiphyseal plate, owing to trauma, and later started to proliferate and become ossified through the activity of the surrounding fibrous tissue. These explanations are more logical than the assumption that disturbance in ossification led to the formation of several bony nuclei in the epiphysis of the femur, which frequently has been pointed out as an explanation of the stage of fragmentation characteristic of Perthes' disease.

*Joint Cartilage.*—The changes in the joint cartilage were so pronounced that in no place could a normal picture be seen. It was evident from the histologic picture that the changes in the cartilage were secondary to the bony alterations in the epiphysis. For this reason the disturbance of the joint cartilage over the lateral pole of the head of the femur differed from that over the medial part. In the upper part of the lateral portion the joint cartilage was mainly separated from the necrotic bone by the subchondral fracture space (fig. 6). In this area all the changes in the joint cartilage, except for slight resorption under a fibrous tissue pannus, can be explained by either primary or secondary traumatic damage to the cartilaginous tissue.

The cartilaginous cover over the medial portion of the head of the femur (fig. 11) showed a different picture, due to the advanced stage of the process of reorganization in this part of the epiphysis. The difference in degree of the pathologic changes was also due to a functional moment, in the sense that the lateral portion was under more static-mechanical irritation than the medial portion. Both portions, however, showed considerable unevenness in the course of the joint cartilage, due to the irregularity of the bony epiphysis following fracture and reorganization.

A fibrous tissue pannus (figs. 6, 7 and 11), which developed from the ligamentum teres and the synovial tissue at the margins of the joint, covered the entire head, except for a small area laterally. The pannus tissue at the medial side was looser and richer in vessels than that on the lateral side. Correspondingly, the resorption of cartilage was more marked on the medial than on the lateral side. This difference may also have been due to the inequality in weight bearing of the two portions of the femoral head.

**Lateral Part of the Joint Cartilage:** The lateral part was composed almost entirely of old hyaline cartilage, with cartilaginous cells which possessed good

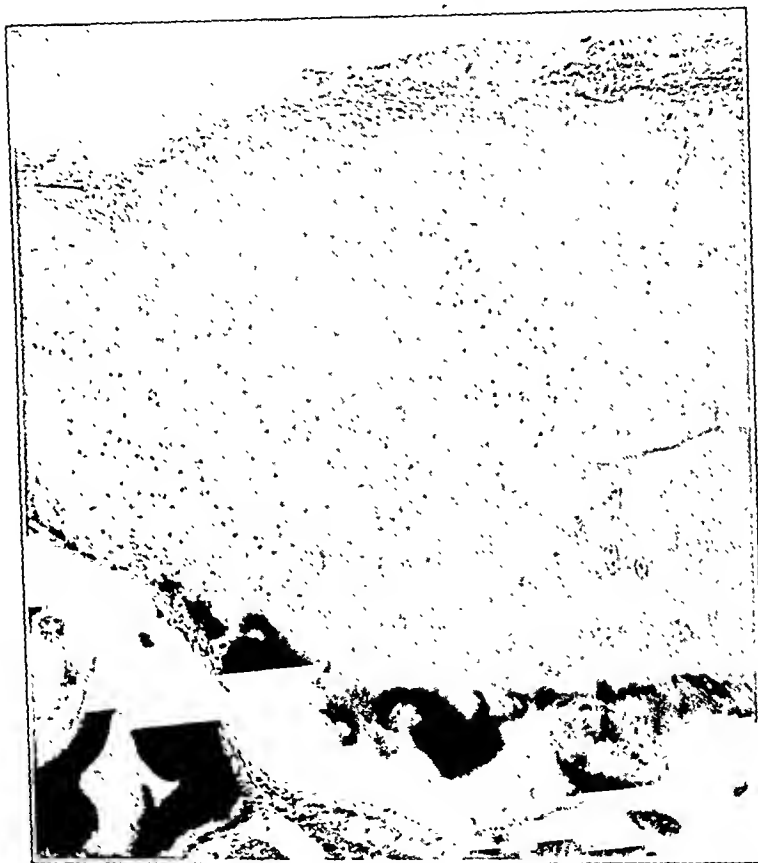


Fig. 11.—Photomicrograph showing formation of joint cartilage over the medial portion of the head of the femur close to the fovea capitis. The old hyaline joint cartilage is fairly well preserved only in the deeper layers. The superficial layers of newly formed primitive cellular cartilage are covered by a fibrous tissue pannus resembling perichondrium. The subchondral bone is regenerated, with hyperemic fatty bone marrow.

nuclear stain but with no signs of normal structure, such as a gliding or pressure layer (figs. 6 and 7). The cartilage was of varied thickness, owing to the degree of cartilage resorption from below. As already mentioned, a subchondral fracture space ran through the spongy bone of the epiphysis, separating the joint cartilage from the bone except for a short distance, where subchondral spongy



bone remained in connection with the joint cartilage. For the greater part, however, the upper wall of the fracture space was observed to be formed of noncalcified cartilage. In the small area where bone was still in connection with the joint cartilage, the zone of calcification could be easily made out. However, all the cartilaginous cells in this zone of calcification and all the spongy bone trabeculae which originated from the lower surface of the cartilage lacked nuclear stain. They as well as the bone marrow cells were necrotic. The necrosis extended into the noncalcified layer of the joint cartilage for a depth of from about three to four layers of cartilaginous cells, whereas all the other portions of the noncalcified cartilage showed good cellular stain. This proved definitely that joint cartilage for the most part obtains its nutrition by diffusion and osmosis of synovial fluid; only the deepest layers of the noncalcified and the calcified cartilage depend on nutrition from the vessels of the bone marrow.

In the area where joint cartilage was still in connection with subchondral bone, thinning from below could not take place, and the joint cartilage was of normal thickness. However, as soon as the subchondral bone was worn off, owing to friction along the fracture surface and noncalcified cartilage borders of the fracture space, thinning could occur. The hyaline cartilage was impregnated with fibrinoid material, which was recognized as a dark red substance within the superficial layers of the cartilaginous tissue. Irregularities, such as fringes or villi, could also be seen on the lower surface of the joint cartilage, which in some places had a brushlike appearance, due to exposure of the collagenous fibrils, which were previously hidden by the ground substance. In other areas the lower surface was ragged and showed many small fissures and tears, which were also impregnated with fibrinoid substance. These fissures were almost all radial, corresponding to the preformed radial structure of this layer of joint cartilage. This process of thinning of the joint cartilage from below was so advanced in some parts that only a few layers of cartilaginous tissue remained. In some areas the process had led to complete interruption of the joint cartilage, with formation of irregular holes. The irregular cartilaginous ends facing the holes also showed fibrillation, impregnation with fibrinoid substance and partial necrosis. A few living cell groups showed proliferation of inconsiderable degree.

The observation of necrosis of cartilaginous cell groups close to the fibrinoid layer was constant. It was clear that this necrosis in the superficial layers of the joint cartilage was of different origin than the necrosis observed in the deepest layers, which remained in connection with subchondral bone. The necrosis in the superficial layers was not due to lack of nutrition, because fluid can easily reach this level of cartilaginous cells. Necrosis was only partial, and normal cell groups could be seen among the necrotic groups. The necrosis of cartilaginous cells in the superficial layers was striking, and as it could not be seen in any other part of the joint cartilage, it was probably due to traumatic damage of the joint cartilage.

The decrease in thickness was caused by simple wearing off of cartilaginous substance by the constant friction of the joint cartilage on the underlying necrotic epiphyseal spongy bone. Active resorption in the sense of a cellular process was impossible in this area, as no living tissue was present to sustain the process. Further proof that only mechanical factors were responsible for the marked unevenness of the joint cartilage on its lower surface was established by the observation that where the joint cartilage was in intimate contact with the epiphyseal plate, permitting two soft tissues to move against each other, the lower surface of the joint cartilage was smooth. This contact between the joint cartilage and the epiphyseal plate was brought about by the entire removal

of the necrotic epiphyseal bone in this area. There, too, the thickness of the joint cartilage was diminished, but this thinning went back to the time when joint cartilage still moved against the underlying bone. As soon as the entire epiphyseal spongy bone disappeared, friction continued between the joint cartilage and the cartilage of the epiphyseal plate, but without much traumatization; thus, the process of thinning the joint cartilage came to a standstill.

Near the lateral pole occurred complete interruption of the joint cartilage, but there the defect was due not to gradual thinning, but, more probably, to fracture. This area in the roentgenogram corresponded to the outer edge of the roof of the acetabulum, which at the time of trauma probably caused this fracture. There, too, a part of the joint cartilage was displaced toward the epiphysis. The ends of the joint cartilage showed again a great number of necrotic cartilaginous cells, which appeared as empty holes in the hyaline ground substance. At the ends of the fracture there was proliferation of cartilaginous cells—an attempt at regeneration—which was not sufficient to bridge the defect in the joint cartilage. At some distance from the fracture space formation of typical primitive hyaline cartilage had taken place along the upper and lower surfaces of the joint cartilage. The defect itself was filled with well vascularized fibrous tissue, which extended into the ends of the cartilaginous fragments and led to their partial resorption. Small strips and bridges of hyaline cartilage remained included in the hyperemic fibrous tissue, which progressively invaded the cartilaginous substance. The picture just described is typical of the healing of fracture in joint cartilage. Experimental observations and a few histologic studies of human material after intra-articular fracture have demonstrated that fracture of joint cartilage never heals by *restitutio ad integrum* but that the repair takes place by means of fibrous tissue, with some cartilaginous proliferation at the ends of the fragments.

**Medial Part of the Joint Cartilage (fig. 11):** On the medial side of the joint cartilage, where a large defect was observed on gross inspection, the cartilaginous cover was of less than normal thickness. This marked thinning was partially due to resorption from below, without adequate proliferation of cartilaginous cells. However, this process was insignificant as compared with the resorption of cartilaginous tissue from above by the fibrous tissue pannus.

**Incomplete resorption of cartilage.** This type of resorption is characteristic of cartilaginous tissue and was described by Weichselbaum and Pommer. The process consisted of cellular activity which removed the ground substance of the old hyaline cartilage but preserved the collagenous fibers. These fibers appeared only after resorption of the hyaline ground substance and were utilized for the formation of the fibrous tissue pannus; thus, an intimate connection existed between the fibrous tissue and the cartilage. At the same time the cartilaginous cell groups opened, and the cartilaginous cells started to proliferate, owing to the better nutrition under the fibrous tissue pannus, and ultimately changed into fibrocytes. The margin of the fibrous tissue pannus along which most of these changes took place usually presented a sharp lacunar or somewhat wavy outline. The lacunae were filled with rather cellular fibrous tissue, which included a few multinuclear chondroclasts. Where fibrous granulation tissue of the epiphysis invaded the joint cartilage from below, producing incomplete cartilaginous resorption, some marginal areas showed a sharp lacunar outline, along which the cartilaginous ground substance disappeared. In other places, however, the disappearance and fading of cartilaginous ground substance into fibrous tissue was more gradual. Where the resorption of the joint cartilage at the site of

the pannus had advanced into the deeper layers of noncalcified cartilage, the lacunar defects became refilled with a more primitive type of hyaline cartilage, which differed sharply from the old cartilage.

The new primitive hyaline cartilage, which was of embryonic character, was rich in cells, irregularly distributed and only occasionally accumulated in large cell groups. The cells were small, resembling fibrocytes and even myxomatous cells, a picture frequently seen in embryonic cartilaginous tissue. The ground substance had a watery, clear blue appearance. This new cartilage was as yet devoid of functional structure in the sense of a superficial gliding and a deep pressure layer. The presence of vessels in the new primitive cartilage indicated that this cartilaginous tissue had developed on the basis of preformed fibrous tissue.

The transition from the mature old hyaline cartilage to the more primitive new cartilage was gradual in some parts, and in other places the differentiation was rather sharply lacunar, resembling the borderline between the fibrous tissue pannus and the old cartilage. In this area it was evident that the new primitive cartilage derived in part from the process of incomplete resorption of the old hyaline cartilage. The collagenous fibers ran directly from the hyaline ground substance of the old cartilage into the matrix of the new cartilage. Small strips of living old cartilage, which had thus far escaped resorption, were seen in the new primitive hyaline cartilage.

These changes were especially marked at the margins of the joint. There was a bony exostosis, covered by a relatively thick layer of young primitive hyaline cartilage, the appearance of which was similar to the newly formed cartilage seen at the site of the defect of the old cartilage near the joint surface. Closer to the margins this new cartilage was still of a fibrous nature and included a number of vessels. The new cartilage was also covered by a pannus of fibrous tissue. The marked marginal proliferation and the quiescence of the joint cartilage over the free joint surface can be explained by the fact that under normal conditions the cartilaginous cells at the margins of the joint were observed to be more active. Some authors call this region the zone of cartilaginous proliferation, from which the joint cartilage grows. This supposition is supported by the fact that similar changes had taken place at the margin of the joint cartilage near the ligamentum teres. This area corresponds to the joint margin around the fovea capitis.

Besides the considerable formation of new cartilage around the ligamentum teres there was an area where, owing to incomplete cartilaginous resorption, the entire thickness of the old joint cartilage had been removed to the zone of provisory calcification. However, the fibrous tissue pannus had changed to primitive hyaline cartilage, which filled the defect. In another area near the fovea capitis the old joint cartilage had been removed entirely, but no new cartilage formation had taken place. Therefore, the surface of the head was covered in this region by only a thin layer of pannus tissue, in the deeper layers of which a few cartilaginous cells had developed in some places. The connection of this fibrous tissue with the underlying bony tissue was of periosteal type. Relatively primitive fibrous bone could be seen at the surface, and the fibers of the pannus were inserted into the fibrous bone like Sharpey's fibers.

The remaining thinned old joint cartilage was living tissue. The cartilaginous cells were irregularly distributed; many of their capsules showed a strong oxyphilic stain, and often oxyphilic granules were present within the cell protoplasm. This process apparently represented a form of cellular degeneration, for often retrogressive changes were observed in the nuclei of these cells, frequently leading to complete disappearance.

The thinning of this medial part of the joint cartilage, however, was not due entirely to resorption from above. Following reorganization of the medial portion of the epiphysis, living bone marrow was again formed on the lower surface of the joint cartilage, and more or less normal conditions were reestablished, so far as a bony lamella was present along the calcified deeper layers of the joint cartilage. The enchondral ossification of the new joint cartilage was a little more extensive but was slightly irregular and led to formation of porotic spongy bone.

If one proceeds from the joint margin along the joint surface one observes three types of thinning of the joint cartilage from below: (1) disappearance of cartilage by enchondral ossification; (2) wearing off of cartilaginous tissue due to friction, and (3) thinning by fibrous granulation tissue, due to the process of incomplete resorption of cartilage.

Arthritis deformans. In the old joint cartilage it was often noted that as the layers of calcified cartilage were removed bone marrow continued to advance into the noncalcified cartilage. Later, the cartilaginous layers over the bone marrow became calcified again and formed a thin, irregular bony lamella. By this gradual progression of the bone marrow into the noncalcified cartilage, however, more and more substance of the joint cartilage disappeared, owing to the lack of cartilaginous proliferation. This invasion of the joint cartilage by marrow spaces, followed by enchondral ossification, which resulted in thinning and even in disappearance of the joint cartilage, must be considered as a pathologic process. Under normal conditions in a growing person, some invasion of the joint cartilage occurs from below, corresponding to the small amount of enchondral ossification in the area shown in these sections. However, the normal process is more regular and does not lead to the steplike invasion of marrow spaces into the joint cartilage.

Under pathologic conditions, such as arthritis deformans, invasion of bone marrow into the joint cartilage occurs as a response of the bone marrow to degenerative changes in the joint cartilage. From the presence of the oxyphilic cell capsules and granules in the area of joint cartilage shown in these sections it is reasonable to assume that the joint cartilage was damaged. Therefore, the invasion from below may be considered to be a sign of juvenile arthritis deformans.

In addition, changes corresponding to the picture of arthritis deformans were observed in the form of joint bodies and marginal exostoses. A small bony body of this type could easily be seen on the lateral part of the joint margin on gross inspection. It lay within the fibrous tissue pannus and had wide marrow spaces, which were filled with fatty bone marrow. The peripheral portion of this body showed a bony layer of lamellar bone tissue on the outer surface, which gradually blended into fibrous osteoid tissue and the fibrous tissue of the pannus. At one end the bony tissue blended into fibrous cartilaginous tissue. This body developed directly in the pannus of the joint margin.

Marginal exostoses were also observed around the whole head. They were somewhat larger on the lateral than on the medial side. They consisted of thin irregular bony trabeculae lying in fatty bone marrow. At their surfaces new hyaline cartilage had formed, covered by a pannus of fibrous tissue.

On the lateral side of the head changes were observed similar to those seen in association with arthritis deformans. The superficial cartilaginous layers were frequently impregnated with fibrinoid substances. This is always a sign of mal-treatment of soft tissue and noncalcified cartilage. This condition frequently can be noted in synovial villi in cases of hypertrophic arthritis. Irregularities in the sense of fringes, villi or fibrillation at the lower surface of the joint cartilage, such as are commonly seen in the similar process of wearing off of cartilaginous substance in cases of hypertrophic arthritis, were absent. Therefore, the impres-

sion was obtained that the hyaline cartilage had preserved a normal amount of elasticity, which prevented fibrillation and degenerative changes in the ground substance.

In primary arthritis deformans the first histologic changes are expected to occur in the superficial layers, where the degenerative changes of fibrillation and fissuring of cartilaginous cells take place typically. In the case reported in this paper the superficial layers showed few changes beside resorption by the fibrous tissue pannus. Despite the fact that considerable deformity of the head of the femur had taken place and the joint cartilage showed many changes, no lesion characteristic of idiopathic arthritis deformans was present, but all the changes must be considered to be secondary.

*Synovial Tissue.*—The arthritic changes in the synovial tissue can be explained on a basis similar to that of the changes in the other structures. The ligamentum teres (fig. 6) represents a strong ligament, made up of fibrous tissue with a few fat cells in the interstitial spaces. The superficial layers had the characteristic appearance of synovial tissue, even to an endothelial cellular layer. The ligament conducted a great number of vessels, some of which showed perivascular round cell infiltration. At the insertion of the ligamentum teres marked structural irregularity was present, mainly due to the advanced stage of bone regeneration. From the synovial cover of the ligamentum teres a fibrous tissue pannus spread over the joint surface, and in some places it joined another pannus, which derived from the synovial tissue of the joint margin. The synovial pannus showed inflammatory changes similar to those described as present in the ligamentum teres. These changes were characteristic of hyperplastic synovitis, but in this region also there was nothing to suggest real arthritis.

Some of these arthritic symptoms may be explained on the basis of synovial irritation, caused by the escape of detritic material from the subchondral fracture space into the joint cavity through small fracture holes in the joint cartilage. This irritation of the joint capsule was capable of causing pain. The little particles which floated in the synovial fluid were easily resorbed from the synovial tissue and either disappeared or became deposited in the synovial membrane, where they often remained for some time, without reaction.

*Epiphyseal Plate.*—The changes in the epiphyseal plate, which were similar to those in the joint cartilage, were due in part to the primary trauma and in part to secondary trauma, resulting from lack of support of the epiphyseal plate at the time when the necrotic bony tissue of the epiphyseal plate was substituted by fibrous tissue.

Fissures and tears of the epiphyseal plate were frequently observed, filled with fibrinoid substances, which also impregnated the margins of the fissures. In some places the epiphyseal marrow spaces close to the epiphyseal plate were filled with primitive hyaline cartilage, which represented herniations of the cartilaginous tissue of the epiphyseal plate. Some marrow spaces of the necrotic part of the epiphysis, however, were filled with fibrous tissue, which could be explained on the basis of the immigration of fibroblasts from the diaphysis through the fissures of the epiphyseal plate.

Besides the marked waviness of the epiphyseal plate, which still may be considered to be normal, there were severe traumatic changes near the medial as well as the lateral pole. Several complete interruptions were observed, with formation of a number of smaller fragments (fig. 7). Similar to the condition in the joint cartilage, there was no regeneration of cartilaginous tissue but only scar formation.

In the lateral part, where the epiphyseal plate was absent for some distance, fibrous tissue, derived from the diaphyseal marrow spaces, filled this defect and continued to grow further into the epiphysis.

*Neck of the Femur.*—The neck of the femur in the area just described showed entirely a pathologic structure. Owing to the lack of the epiphyseal plate no primary spongiosa could be seen in this area. This large defect in the diaphysis was filled with an irregular network of fibrous bony trabeculae in the fibrous tissue stage of bone formation. The trabeculae lay within loose fibrous bone marrow, which was connected with the fibrous tissue of the epiphysis. There was no doubt that the condensation of bony tissue around the defect was due to the pressure exerted on this area by the outer edge of the roof of the acetabulum. On the whole this area of spongy bone was cut off sharply at the level which corresponded to the junction of the cartilaginous plate and the spongy bone of the metaphysis. The whole picture was one of scar formation. The bony tissue, although still irregular, indicated a tendency to complete restoration.

The partial destruction of the epiphyseal plate led to early synostosis between the epiphysis and the diaphysis in this area and would certainly have caused disturbance in growth. This change, in a slightly more advanced stage, could be seen on the medial side, where, as mentioned before, complete fracture of the epiphyseal plate had also occurred. At this point the marrow spaces of the epiphysis and those of the metaphysis communicated with each other; new bone tissue, in the form of rather thick bony trabeculae, ran continuously from the epiphysis into the metaphysis, filling the defect in the area of interruption.

### CONCLUSION

The purpose in this article was to describe a case in which severe trauma to the hip joint was followed by changes in the upper epiphysis of the femur which clinically, roentgenologically and histologically resembled those of Perthes' disease to the minutest detail. Only one point does not quite fit into the typical picture of Perthes' disease, namely, the patient's age—13 years—at the time of trauma. In most cases Perthes' disease occurs between the ages of 5 and 7 years.

This case, however, was also of interest because of the marked arthritic changes of degenerative and traumatic nature which developed after the injury. These alterations were caused by the deformation of the head of the femur and by secondary trauma as a result of continued weight bearing and joint movements.

These observations, therefore, speak in favor of the traumatic etiology of Perthes' disease. Since, however, a history of severe trauma is not found in all cases of Perthes' disease, one must consider that frequently repeated minor traumas, such as occur in daily life, may also cause aseptic necrosis of the epiphysis, with insidious clinical onset.

# AN INVESTIGATION INTO WIRING OF THE SPINOUS PROCESSES AS A MEANS OF INTERNAL SPINAL FIXATION

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The three great needs to be recognized in the treatment of tuberculosis of the spine are: first, support of the superincumbent weight, namely, that of the head, shoulders and arms, away from the carious and softened vertebral bodies; second, some form of posterior leverage to throw the weight of the upper part of the body on the posterior and lateral aspects of the spine, and third, some form of fixation until ankylosis has occurred so that arrest of the disease and healing may ensue.

The aim of curative measures is to secure ankylosis, for in its absence there is no certainty that relapse may not occur. The choice of method today lies between nonoperative measures (external splinting) and operative procedures (internal splinting).

While it is true that under favorable conditions by the use of conservative measures, such as the convex frame for the recumbent patient, or the plaster-of-paris jacket, the steel spinal brace or some modification for the ambulatory patient, deformity at times is prevented and lessened, nevertheless mechanical treatment is admittedly a tedious and difficult procedure, and occasionally a quite ineffective one, because of the difficulty or impossibility of securing absolute immobility in certain regions.

These insufficiencies, along with the burdensome care required for casts and braces over an indefinite period for the arrest of the diseased process, prompted the search for some method of internal fixation which not only would meet the necessary mechanical requirements but would shorten the duration of the disease, promote healing and remove the inconvenience of prolonged external fixation.

It would appear that the first operation for this purpose was suggested in 1891 by Hadra, who proposed wiring of the spinous processes in cases of Pott's disease, after the successful use of this method in a case of vertebral fracture. He described his procedure as follows:

The large muscles on either side are longitudinally incised and retracted. Then with a strong curved needle carry silver wire through the interspinous spaces

above and below the spinous processes to be wired, in a figure-of-eight fashion, as often as is desired, and fasten the ends by twisting.

In 1896 Calot endorsed Hadra's views and recommended his procedure after forcible rigid correction by a method which was elaborated by himself and widely tried out but which was short lived because of the attendant high mortality.

A similar and more comprehensive operation, in that the deformity was first corrected and the adjacent spinous processes denuded and bound together by silver wire, was described by Chipault in 1893, and again in 1900, when he reported successful treatment by his method in a case of tuberculosis of the seventh dorsal vertebra with compression of the spinal cord and resultant paraplegia in a child  $4\frac{1}{2}$  years of age. He contended at that time that metallic agents of fixation not only acted mechanically but also excited periosteal proliferation and thus stimulated ankylosis of the posterior part of the spine.

Lange in 1902 implanted steel wire on each side of the spinous processes with apparent success until the movements of the spine caused a protrusion of the wire ends through the skin and they had to be removed. After much research, he found tin-plated steel to be the best material. In 1908 he operated successfully on a boy of 12 years and reported the case two years later. The disease was at about the tenth dorsal vertebra, and the splints were of heavily tin-plated steel wire, 10 cm. long and 5 mm. thick. Incisions were made through the skin and fascia which corresponded to the upper and the lower end of the splints; the splints were then inserted beneath the muscles on either side of the diseased vertebra and the bulbous ends attached to the spinous processes by silk. After the external support was removed, the patient went to work as a blacksmith's helper, the metal plates remaining in situ and holding the diseased section of the spine securely.

Internal fixation by bony ankylosis, surgically produced, was first realized and reported by Albee, on May 15, 1911, when he suggested a method of spinal fusion. This was followed by a report of Hibbs on May 27, 1911, on the successful use of spinal fusion. In September of the same year Albee reported the bone graft procedure that now bears his name. He stated:

A bone graft is far superior to an internal metal splint, because by following Wolff's Law it will become thicker and stronger if necessary to hold the weight and strain brought upon it, whereas in the case of an internal metal splint, no dependence can be placed on it to hold the weight or strain, because of bone atrophy and absorption which takes place directly around the metal.

The report of the commission to investigate the results of operations on the spine for ankylosis and the many reports by individual workers (for which see bibliography) have attested the indisputable value of these methods.



Throughout this entire period, the only report on internal fixation of the spine by metal is that of Lange in 1927, who recorded the results in fifty-two cases of Pott's disease. In all but five successful fixation was obtained by the use of celluloid splints, from 10 to 30 cm. in length, depending on the length of the area to be fixed, which were curved carefully to fit the kyphos deformity, the splints being placed on both sides of the spinous processes and held in place by double loops of silk. The results in five cases were unsuccessful owing to failure to fit the splint to the gibbus, so that the ends broke through the skin and had to be removed.

Lange reported the successful use, since 1924, of rust-proof steel splints fixed to the spinous processes by steel wire.

The applicability of the methods of Albee and Hibbs are undeniable. Posterior spinal fixation is indicated when either injury or disease has caused or is causing destruction of one or more vertebrae. Since it acts only by leverage and stabilization and does not of itself remove disease tissue, it is in the nature of a splintage.

Procedures to obtain fusion of the bone must be supplemented by efficient external fixation and support until firm ankylosis occurs.

The ideal method must provide immediate fixation, for until this occurs, motion of the diseased parts, as due to respiratory or abdominal excursions, cannot be eliminated.

Perhaps this might be anticipated by the metallic binding of the spinous processes by wiring, much as in the method suggested by Hadra in 1891. No effort has ever been made to prove or disprove his contentions, largely because of the ill repute into which internal metallic fixation has fallen during the past two decades in the controversy over its use in fracture work.

We determined (1) to investigate the reaction of bone and its surrounding tissues to metals that we believed might be satisfactory for such a purpose; (2) to prove the mechanical efficiency of such a fixation procedure as Hadra had suggested, and (3) to study the reaction of bone and the surrounding tissues under the conditions created by this procedure.

#### THE REACTION OF BONE TO METALS

*Review of the Literature.*—The majority of the investigations of the reactions of bone to metal have resulted from the controversy that has been maintained ever since Lane and his followers widely sponsored internal metallic fixation in 1905. A large group (see bibliography), led by Albee, condemn its use, while a smaller but just as enthusiastic group (see bibliography), led by Lane, endorse its use and show excellent results.

The earliest reference to the use of wire for suturing a fracture is that of Icart in 1775. Levert in 1829 performed the first extensive series of experiments on dogs to determine the tolerance of soft tissues to metallic sutures applied about arteries, using gold, silver, lead and platinum and finding the latter least irritating. In 1840 Malgaigne presented his hooks, later modified by Levis, Otis and Duplay; Gaillard, his screw in 1865, and Senn, the metal ferrule in 1893. Thiriar presented the aluminum plate in 1894, Estes the steel plate in 1887 and Streinach the silver plate in 1900, while in 1902 Lambotte reported his work with brass plates and copper and iron wire. The greatest impetus to internal metallic fixation of fractures was the work of Lane, first reported in 1905.

One of the most complete studies to ascertain the reaction of bone to metal was a brilliant investigation by Hey-Groves in 1913, whose conclusions were as follows:

1. Metallic magnesium, when used as a peg, acts as a powerful stimulus to the formation of bone.
2. Indifferent aseptic foreign bodies in the tissues have no ill effects on healing.
3. Nickel-plated steel is well accepted by the tissues.

Blake in 1912 noted that copper wire or plate appeared to set up irritation and to lead to inhibited healing. Trout in 1915 inserted steel screws in the bones of young rabbits and noted inhibition of bone growth. In 1916 Mann carried out a short series of experiments on dogs to determine the tolerance of joints to steel nails and screws, finding them well embedded in four weeks. In 1918 Leriche and Policard concluded that the steel plate of Lambotte retarded repair and inhibited osteogenesis and advised the use of less noxious metals, such as aluminum, magnesium, silver and gold.

Zierold in 1924 reported the following conclusions, after utilizing a large series of animals and a great variety of metals with careful pathologic studies:

1. Gold, aluminum and stellite are readily tolerated by bone and act as inert material, contrary to the finding of Duval, Elsberg and Danborn, who observed that aluminum was absorbed.
2. Silver and lead are only slightly less tolerable to bone but are easily corroded and evoke a slightly greater response of the connective tissue.
3. Zinc goes into solution readily and interferes with the regeneration of the bone.
4. Nickel is injurious to bone growth, contrary to the findings of Hey-Grove.

5. Magnesium retards rather than accelerates the production of bone.

6. Copper definitely stimulates the production of bone, contrary to the findings of Blake.

7. Copper aluminum bronze frankly interferes with the regeneration of bone and tends to become extruded.

8. Steel and, to a lesser degree, iron inhibit the regeneration of bone.

Cunéo and Rolland, Young and Blake found that metal plates were not deleterious to bone or to bony union. Others (Magie; Stanley and Gatellier) noted that metallic bands stimulated the formation of callus. Collins, in a series of tests on rabbits with experimental fractures, noted marked callus response to bands made of gold, silver, nickel and copper. On the other hand, Brickner, Frank, Freeman and Lathrop experienced nonunion, softening and necrosis of the bone.

Gazzoti in 1923 buried small cylinders of various metals in the tibias and femurs of dogs. Iron and copper were found to rust and tarnish. Nickel and tin persisted practically unmodified, the latter being found especially favorable for bone tolerance.

In 1926 Fründ attributed the aseptic suppuration about metal objects to the galvanic currents arising between the two metals of which many metal objects are composed. He reported the absence of suppuration with nails of rustless steel, i. e., a single metal; his conclusions differed from those of Lange, who in 1910, experimenting with a great variety of metals, had found that those readily oxidized by the body fluids (iron, copper, zinc and nickel) are likely to cause aseptic suppuration of the tissues, rendering healing difficult, and to lead to extrusion of the foreign body. Tin-plated steel was found to be the metal best tolerated.

Rugh in 1928, experimenting with the bactericidal action of various metallic substances, concluded that metals such as tin, gold, platinum and silver cause less reaction in the body tissues, making the tissues less liable to infection than if more irritating metals are used.

Bohlman in 1929, using a great number of metals and other foreign bodies, introduced in the region of the epiphysal cartilage plate of growing bones, noted tolerance but resultant shortening due to inhibition of the growth faculties. Robineau and Contremoulins and Robineau and Moruzi are cited by Ichok in 1929 as demonstrating osteosynthesis in fractures with metallic bands of aluminum bronze, immovably fixed. Ichok drew attention to absolute fixation as the prime essential condition of good tolerance.

More recently Verbrugge (1933) reported the experimental use of magnesium. He found it absorbable in one year's time, nontoxic, well tolerated by bone and stimulative to the formation of callus. In 1934

he reported a number of cases of fracture in human beings in which magnesium and an alloy of magnesium and aluminum were used in internal fixation, both metals absorbing after good union had occurred, and his other experimental findings were well borne out.

Ménégaux, Möyse and Odiette (1934) studied metals and their effect on cultures of bone tissue and connective tissue in vitro in accordance with the method of Carrel. They concluded that the extremely toxic metals, arranged in descending order, are copper, magnesium, iron, aluminum bronze and soft steel. In the slightly toxic group they place zinc, silver, tantalum, tin, nickel and tungsten, and in the indifferent group, the harmless metals, gold, aluminum and lead.

*Methods of Investigation.*—It was our intention to investigate only those metals which have been found acceptable to the body tissues by previous investigators and which in wire form might be suitable for fixation of several spinous processes.

We were especially desirous of studying two copper wire alloys—one, everdur, an alloy of copper (96 per cent), silicon (3 per cent) and manganese (1 per cent); the other, beryllium copper, containing 2.25 per cent of beryllium. Both were of remarkable strength, of high resistance to corroding substances and, we believed, readily adaptable in the soft annealed wire form for our purpose. We wanted to compare the effects of these metals on bone with those of copper, tin, magnesium, lead and steel. Other metals were considered impracticable for our purposes.

Rabbits were utilized throughout this series of experiments (series 1). With the animals under ether anesthesia, the outer side of the thigh or leg was shaven and prepared with iodine and alcohol. Under best aseptic conditions, a 2 inch (5 cm.) incision was made through the skin and fascia, parallel to the long bone, the muscle split down to the bone and the tissues freed over an area of about  $\frac{1}{2}$  inch (1.27 cm.). Where the copper alloy wire was used, a hole was drilled through the bone, the sterilized wire inserted and the ends brought together by twisting.

In the case of the copper, magnesium, tin, lead and steel, metal bands were wound about the exposed shaft of the bone. The fascia and skin were closed in separate layers. The entire procedure rarely lasted over ten minutes. At the end of variable periods, autopsy was performed, and the bone was studied by the roentgenologist and by the pathologist.

*Comment.*—Not all animals in which a steel strip had been used survived long enough to warrant roentgenographic or pathologic study, but the experiments were not repeated, because so much work had been done by others.

It is noteworthy that in the examination of rabbits that died several days after operation, in which copper, lead, tin and steel had been utilized, there was a marked inflammatory reaction of the soft tissues about the metallic foreign body, so that the latter became embedded in a mass of purulent-like material. This reaction disappeared after many

TABLE 1.—Results of Series 1

Rabbit No.	Metal	Site	No. of Days	Röntgenographic Picture	Gross Pathologic Picture	Microscopic Pathologic Picture
1 (control)	.....	Femur	...	See figures 2 and 4		
2A	Everdur wire ( $\frac{1}{32}$ inch)	Femur	138	Proliferation of bone with spur formation; slight absorption adjacent wire (fig. 2)	Marked proliferation of bone; large posterior spur; no necrosis (fig. 1)	Proliferation of bone
2B	Everdur wire ( $\frac{1}{32}$ inch)	Femur	82	Proliferation of bone; slight absorption, but none about wire (fig. 2)	Proliferation of bone with early spur formation; no necrosis; (fig. 1)	Proliferation of bone
3	Beryllium copper ( $\frac{1}{32}$ inch)	Femur	82	Proliferation of bone; slight absorption about wire (fig. 2)	Proliferation of bone; no apparent necrosis (fig. 1)	Proliferation of bone
4 (control)	.....	Tibia and fibula	...	See figure 3		
5	Copper ( $\frac{3}{4} \times \frac{1}{8} \times \frac{1}{16}$ inches)	Fibula	178	Marked absorption of bone about band; proliferation between tibia and fibula (fig. 3)	Marked necrosis of bone adjacent to metal; band covered with heavy greenish-black deposit	Necrosis of bone
6	Copper ( $\frac{3}{4} \times \frac{1}{8} \times \frac{1}{16}$ inches)	Tibia	58	Thickening of cortex; mottling of bone due possibly to metallic deposits (fig. 3)	No gross changes; bone cut with lessened resistance; bone stained by greenish deposit, punctate in areas; same metal as in rabbit 5	Necrosis of bone
7	Magnesium	Femur	168	Irregular areas of rarefaction on lateral aspect (fig. 4)	Pronounced atrophy of cortex with many areas of necrosis of punched-out appearance; metal band absorbed	Necrosis of bone
8	Tin	Femur	43	No evident changes (fig. 4)	Atrophy and discoloration of bone at site of metal; band covered with white deposit	No change
9	Lead	Tibia	65	No evident changes	No gross changes	No change

weeks, for it was absent in the animals which came to autopsy later, in which the same metals had been employed. The reaction occurred at no time with the copper alloys.

The tendency to osseous destruction seemed directly related to the development and deposit of metallic salts, being most marked with the copper bands, less so with the tin and lead and least noteworthy with the copper alloys. The exact nature of these salts could not be ascertained because of the insufficient quantity of the deposit for satisfactory chemical analysis. One may, at least, hypothesize on the nature of these salts and their importance.



Fig. 1 (series 1).—Photograph of specimens from rabbits 2a, 3 and 2b, respectively. Note the bony proliferation in all specimens. Everdur wire was used on the upper specimen, which was examined after one hundred and thirty-eight days; beryllium copper wire, on the middle specimen, which was examined after eighty-two days, and everdur wire, on the lower specimen, which was examined after eighty-two days.

The metallic copper may form green cupric hydroxide by oxidation in the presence of water, and this salt may in turn lose water to produce black cupric oxide or combine with an acid radical (sulfate, acetate, chloride and proteinate) to form a green basic salt.

Tin is coated probably with white oxide and lead with black oxide. Verbrugge expressed the belief that magnesium is absorbed as the hydroxide.

The matter of toxicology and the importance of these salts in necrosis of bone become an important problem for investigation by the pharmacologist and physiologic chemist.

*Conclusions (Series 1).*—Everdur wire and beryllium copper wire stimulate osteogenesis. There is little tendency to atrophy and necrosis of bone, and this was found in the earlier specimens.

Copper encourages necrosis of bone, which is widespread.

Magnesium is absorbed by the tissues and leads to atrophy and necrosis of bone.

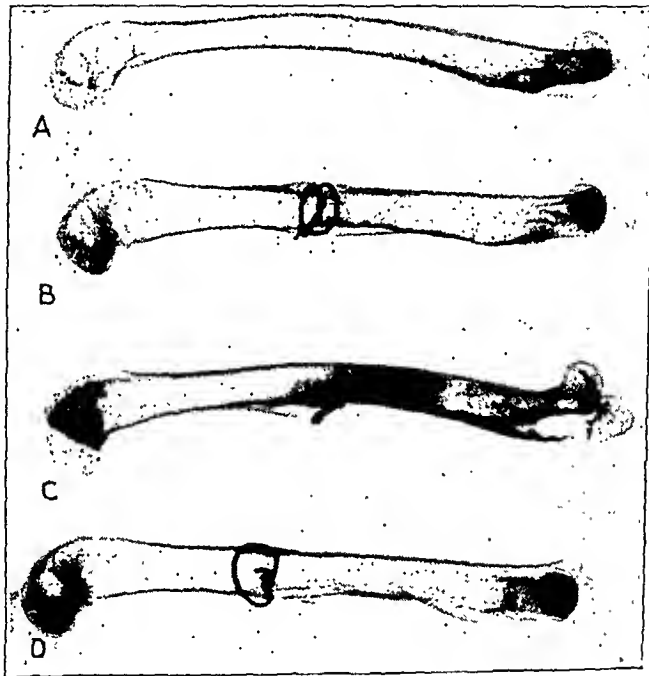


Fig. 2 (series 1).—*A* shows a normal femur; *B*, a femur after fixation with beryllium copper wire for eighty-two days; *C*, a femur after fixation with everdur wire for one hundred and thirty-eight days, and *D*, a femur after fixation with everdur wire for eighty-two days.

Tin, likewise, encourages atrophy and necrosis of bone.

Lead acts indifferently, tending to inhibit normal proliferation of the adjacent periosteum, leading thus to atrophy.

The stage of necrosis seems related in some way to the formation of metallic salts deposited in the metal and in the adjacent tissues. In the case of rabbit 6 (copper), the finding of widespread deposits of minute metallic particles suggests that this may be a possible factor in necrosis of bone.

DETERMINATION OF THE MECHANICAL EFFICIENCY OF WIRING  
OF THE SPINOUS PROCESSES

We believed ourselves justified in using everdur and beryllium copper for the wiring of the spinous processes of dogs, because of the proved tolerance of these metals by the tissues in series 1, as well as their mechanical attributes already referred to. This procedure was as follows:

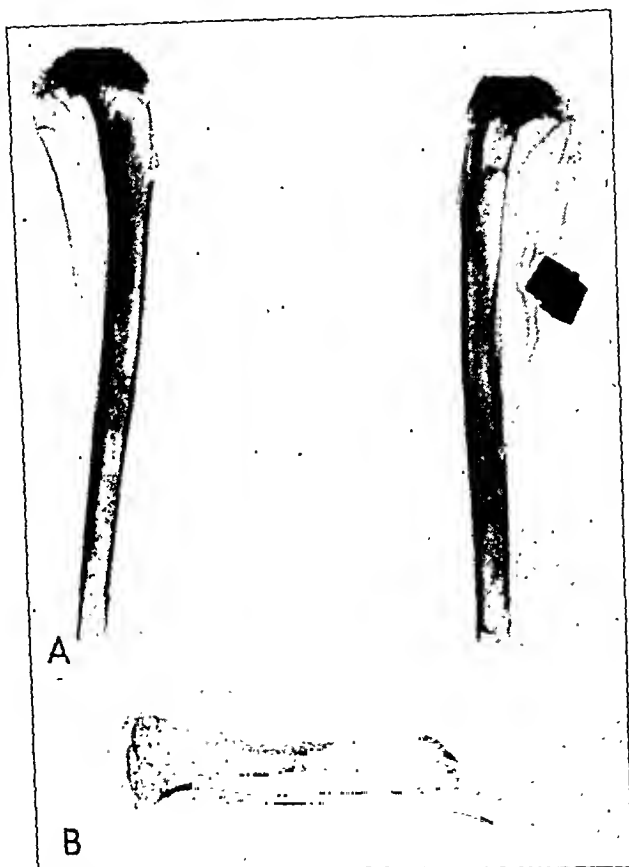


Fig. 3 (series 1).—*A* shows a normal tibia and a tibia after fixation with a copper band for one hundred and seventy-eight days, and *B*, a tibia after fixation with a copper band for fifty-eight days.

1. The animal was anesthetized with ether. The skin in a wide area over the selected site of operation (lower part of the thoracic portion of the spine and the upper part of the lumbar portion) was shaven, prepared with iodine and alcohol and surrounded with aseptic draperies.

2. An incision was made directly over, and long enough to expose, four or five of the spinous processes. The flaps were reflected to each side.



3. The deep fascia was incised along both sides of, and parallel to, the spinous processes, thus preserving the supraspinal and interspinal ligaments.

4. With a dissector, the erector spinae muscles on each side were drawn aside. Bleeding was controlled with hot packs.

5. With the muscles widely retracted, a hole was made with a hand drill through the spinous process of three or four vertebrae and threaded with the selected wire, rewoven several times, the wire not passing between the spinous processes at any time. The free ends were twisted together, cut short and buried deeply.

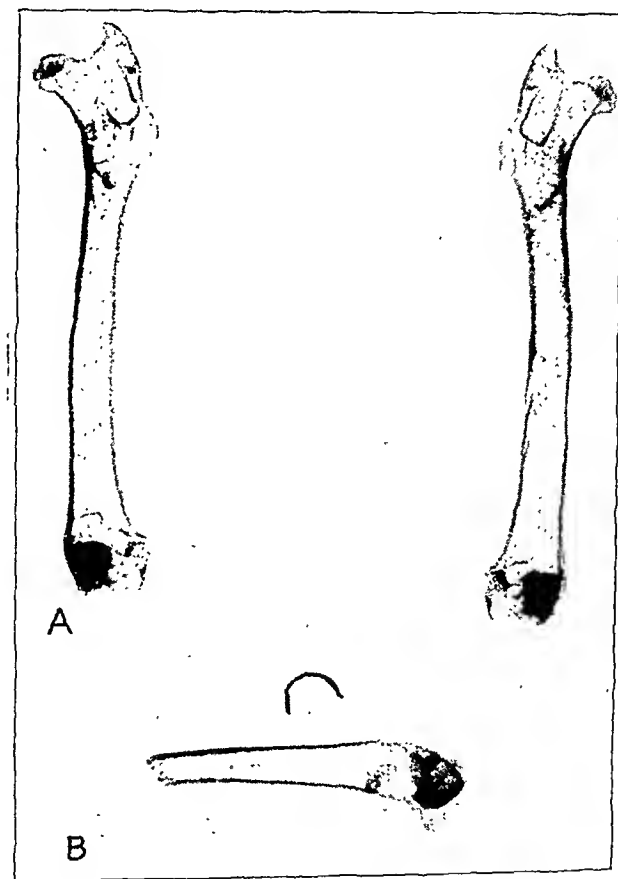


Fig. 4 (series 1).—*A* shows a normal femur and a femur after fixation with a magnesium band for one hundred and sixty-eight days, and *B*, a femur after fixation with a tin band for forty-three days.

6. The muscle mass was permitted to fall into place on both sides, and the fascial incisions were sutured with no. 2 chromic catgut.

7. The skin was closed with interrupted silk sutures and dressing applied. No external fixation was used.

The entire operation was easily and rapidly completed, the duration of the actual surgical procedure rarely exceeding from twenty to twenty-five minutes.

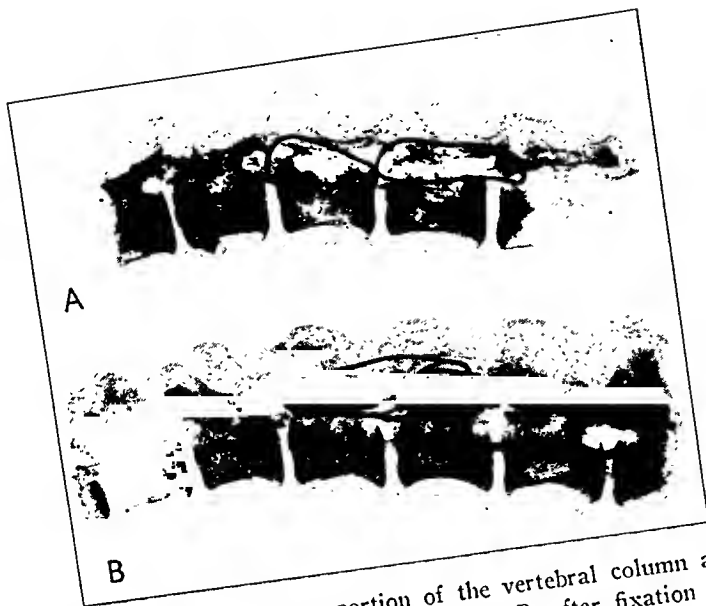


Fig. 5 (series 2).—*A* shows a portion of the vertebral column after fixation with beryllium copper wire for sixteen days, and *B*, after fixation with everdur wire for forty-nine days.

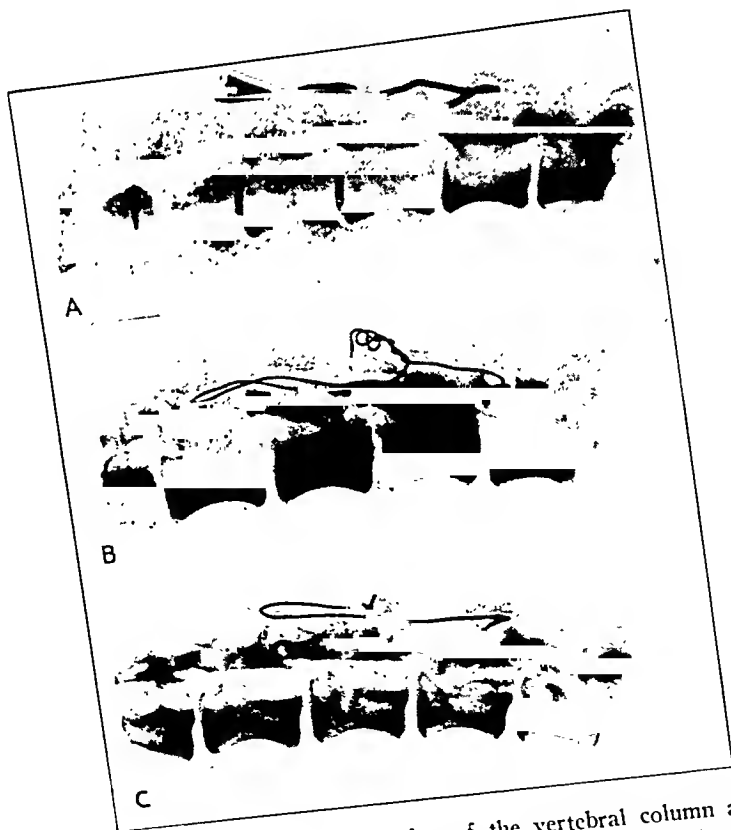


Fig. 6 (series 2).—*A* shows a portion of the vertebral column after fixation with beryllium copper wire ( $\frac{1}{16}$  inch) for sixty-four days; *B*, after fixation with everdur wire for eighty-nine days, and *C*, after fixation with beryllium copper wire for one hundred and twenty days.

Eight dogs were operated on, with three deaths. One animal, the previous subject of many experimental bronchoscopies, died two days after operation. There were no clarifying evidences at autopsy. Another dog, only 12 pounds (5.4 Kg.) in weight, had been the subject of previous hematologic experimentation. While the blood picture was normal, the procedure was apparently too shocking, and he died on the operating table. The third dog died sixteen days after operation, owing to a spastic paraplegia, the result of a technical error, the drill having penetrated the spinal canal.

The two dogs that died shortly after operation were subjected to autopsy, the segment of the spinal column that had been wired was removed, and its mechanical efficiency was determined. There was almost complete absence of motion in all directions, despite the fact that all the musculature had been removed as well as the connections to the thoracic cage and the abdominal wall.

In the remaining five dogs the segments removed for study evidenced increasing motion in direct proportion to the duration of the wiring. The reason for this becomes evident on pathologic and roentgen examination.

To ascertain the mechanical efficiency of the wiring procedure further, in each of two cadavers five spinous processes were fixed with wire  $\frac{1}{32}$  inch (0.08 cm.) in diameter. We had found that wire of larger diameter ( $\frac{1}{16}$  inch [0.16 cm.]) was difficult to mold into place and therefore impracticable for our purpose. Almost the entire thoracic and lumbar portion of the spine was removed with the attached ligaments and muscle mass. The attachments to the scapula, cervical portion of the spine, thoracic cage, abdominal wall, pelvis and lower extremities had to be sacrificed; yet despite the removal of their added fixation, there was relatively no motion in the part of the spine that had been wired, in flexion, extension, lateral motion or rotation, when contrasted with a similar segment that had not been wired.

External fixation, in the form of a body cast, was applied to the last dog (no. 6) operated on to ascertain by periodic roentgen studies whether such superimposed fixation might alter the bony changes.

*Conclusions.*—The operation of wiring the spinous processes of the vertebrae, using wire of everdur and beryllium copper  $\frac{1}{32}$  inch in diameter as a method of internal spinal fixation, is technically simple and rapidly performed.

The mechanical efficiency of the method, i. e., immediate fixation, as determined directly after operation on dogs and on the cadaver, is almost absolute.

There is danger of mortality from shock and from injury to the cord if the spinal canal is entered.

#### REACTION OF THE BONE (VERTEBRAL) TO THE METAL UTILIZED IN THE WIRING OPERATION (SERIES 2)

The results of this study on six dogs are presented in table 2.

*Comment.*—In all of these animals the wire within the canal was found to be unchanged, while that portion outside of the bone and embedded in the soft tissues was covered with a thin dark deposit

TABLE 2.—Results of Series 2

Dog No.	Metal Wire	Vertebrae	No. of Fixation Days	External	Röntgenographic Picture	Gross Pathologic Picture	Microscopic Pathologic Picture
1	Beryllium copper (1/32 inch)	First, second and third lumbar	16	None	No proliferative or degenerative changes (fig. 5)	No evidence of necrosis or proliferation; the canal drilled through the spinous process of the third lumbar vertebra had penetrated the spinal canal and injured the cord	No necrosis of bone
2	Everdur (1/32 inch)	Second, third and fourth lumbar	49	None	Early absorption around wire passing through fourth lumbar vertebra (fig. 5)	No gross evidence of necrosis or proliferation of bone	No necrosis of bone
3	Beryllium copper (1/16 inch)	First, second and third lumbar	61	None	The wire through the fourth lumbar vertebra had pulled out and lies posteriorly; large area of absorption around the wire through the first lumbar vertebra and varying degrees in the second and third lumbar vertebrae (fig. 6)	Evidence of necrosis of bone about the canals through which the wire passes; no proliferation; exposed wire embedded in fibrocartilaginous formation	Necrosis of bone
4	Everdur (1/32 inch)	Eleventh and twelfth thoracic; first and second lumbar	89	None	Marked absorption of bone about wire with-out evidence of proliferation (fig. 6)	Necrosis of bone about wire; no proliferation; exposed wire embedded in fibrocartilage	Marked necrosis of bone
5	Beryllium copper (1/32 inch)	First, second and third lumbar	120	None	Absorption of bone at sites of passage of wire (fig. 6)	Marked necrosis along course of wire through the bone; wire embedded as in dog 4	Marked necrosis of bone
6	Everdur (1/32 inch)	First and second lumbar	30	Plaster body cast	Absorption of bone at sites of passage of wire (4 mos. postoperatively)		

(oxide?), which was readily removed. There was no other appreciable change in the wire, even in the later specimens.

Motion in the wired segments became increasingly evident with the age of the specimen and the degree of necrosis present. It was absent in dogs 1 and 2, slightly evident in dog 3 and present in all directions in dogs 4 and 5.

*Conclusions (Series 2).*—There was no evidence of destruction or proliferation of bone induced by either beryllium copper or everdur wire during the early period, in which the animal remained relatively quiet and in which motion of the vertebral column was at a minimum. The longer the dog was permitted to survive, the greater was the evidence of absorption of bone, roentgenographically and pathologically, about the wire, and that was most marked in the terminal spinous processes, where stress was likely to be most severe. The absorption of bone was greater about the thicker wire.

The wire outside of the bone had become embedded in a mass of new fibrocartilaginous formation but evidenced no apparent change except a slight deposit of oxide.

The motion elicited in the wired vertebral segments was increasingly manifest the longer the dog was permitted to survive.

External fixation (casting) predisposes to more rapid and extensive bony necrosis. This is, possibly, related to the demineralization associated with immobilization.

#### RÉSUMÉ

The copper alloy wires utilized during this investigation were well tolerated by the tissues in the absence of stress and trauma. They apparently stimulate osteogenesis, in contrast to bony necrosis induced by bands of copper, lead, tin and magnesium. The rôle of metallic salts and the direct deposit of minute metallic particles in destruction of bone merit further investigation.

The wiring of the spinous processes as a means of attaining immediate internal fixation, a factor absent in the present methods of spinal fusion for tuberculosis of the vertebrae, is easily and readily performed and early is mechanically efficient. However, with the forces of stress brought to bear between the bone and the wire by the motion of the vertebral column, even despite external fixation, there are rarefaction and necrosis of bone and consequent loss of internal fixation.

The purpose of the procedure is therefore defeated, in contrast to extra-articular arthrodesis, in which internal fixation becomes increasingly secure and effective, in accordance with Wolff's law.

Dr. Richard Manges-Smith made the roentgenographic studies and Dr. Marshall M. Lieber, the pathologic studies.

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# EXPERIMENTAL PULMONARY ABSCESS

## II. TRANSMISSION OF THE DISEASE TO DOGS BY THE BRONCHIAL ROUTE

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Surgeons who have devoted many years to the study of pulmonary abscess are confronted with numerous difficulties in the diagnosis and treatment of this disease.<sup>1</sup> Any aid which the laboratory can furnish will necessarily depend on an increase in the knowledge of its etiology and pathogenesis.

In another communication<sup>2</sup> a method is described for the experimental production of pulmonary abscess in Java monkeys (*Macacus irus*) by the bronchial route. Pus from guinea-pigs containing various anaerobic bacteria, including several types of fusiform bacilli, *Bacterium melaninogenicum*, anaerobic nonhemolytic streptococci, gram-negative motile rods of the *Bacteroides* group and spirochetes, was injected intrabronchially and the corresponding bronchus was then blocked by means of a plug of agar. Of fourteen monkeys thus treated, large abscesses developed in six, pneumonia with several small abscesses of the lung in one and pneumonia and purulent bronchitis with bronchiectasis in one. The remaining animals were essentially normal. These results resemble those of Smith,<sup>3</sup> who worked on rabbits, guinea-pigs and mice.

The present communication describes the transmission of the disease to dogs by the same method.

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From the Research Laboratories and the Department of Pathology of the Mount Zion Hospital and the Division of Thoracic Surgery of the University of California, service of Dr. Harold Brunn.

1. Brunn, H.: Lung Abscess, *J. A. M. A.* **103**:1999 (Dec. 29) 1934.

2. Weiss, C., and Shevky, M. C.: Studies on Experimental Pulmonary Abscess: I. Transmission of the Disease to Monkeys by the Bronchial Route, *Arch. Path.*, to be published.

3. Smith, D. T.: Oral Spirochetes and Related Organisms in Fuso-Spirochetal Disease, Baltimore, Williams & Wilkins Company, 1932.

## MATERIALS AND METHODS

Mongrel dogs, weighing from 7 to 10 Kg., were employed after having been subjected to several weeks of quarantine during which time they were observed for signs of spontaneous infection. The animals were kept in individual cages, and several of them were inoculated against distemper with an antigen obtained from the Cutter Biological Laboratories. A few (series A, table 1) were given intrabronchial pus removed from abscesses of the gums and scrapings from the margins of the gums of persons with active pyorrhea. This material was injected immediately on removal from the body and with the least possible delay. It was kept warm in a thermos bottle, *a seal of petrolatum being employed to prevent the death of anaerobic micro-organisms*. Other dogs (series C, table 2) were given injections of pus removed from abscesses in the inguinal region of guinea-pigs.<sup>2</sup> These lesions, which contained various micro-organisms, including *Bact. melaninogenicum*, several types of fusiform bacilli, anaerobic nonhemolytic streptococci, gram-negative motile rods of the *Bacteroides* group, spirochetes, etc., were produced by inoculating bits of pulmonary tissue removed at operation by Dr. Harold Brunn from a patient with chronic abscess of the lung. At frequent intervals the material was passed in series from one guinea-pig to another, as suggested by Kline<sup>4</sup> and Smith.<sup>3</sup> A third series of dogs (table 3) were given injections of combinations of pure cultures of various anaerobes and aerobes, suspended in a menstruum of viscous starch solutions, a technic developed by Terrell, Robertson and Coggeshall<sup>5</sup> in their researches on pneumococcic pneumonia.

*Technic of Inoculation.*—The animals received no food on the day of inoculation. After cleansing the mouth and pharynx, the larynx was painted with 2 per cent of para-normo-butylaminobenzol-di-methylamino-ethanol hydrochloride in order to abolish temporarily the cough reflex. With the aid of a Jackson bronchoscope (children's size) and a radiopaque ureteral catheter (no. 5), the material was injected directly into the desired lobe of either lung. In the experiment with the pus from guinea-pigs, 2 cc. of melted agar, previously cooled to 40 C., was immediately introduced through the catheter in order to block the bronchus and prevent the escape of the infectious material. The animals were held in a vertical position for several minutes before being returned to their cages.

*Experimental and Clinical Records.*—Roentgenograms, including lateral and posterior views, were taken of all animals before injection and at frequent intervals thereafter.<sup>6</sup>

The rectal temperature and the white blood cell count were recorded at frequent intervals, and observations were made as to appetite, cough and general behavior. At suitable intervals animals were killed for examination. Cultures were made of the heart blood and of the various portions of the lungs.

## SUMMARY OF RESULTS

As seen from table 1, in two of three dogs given injections intrabronchially of pus removed from persons with active pyorrhea pulmonary suppuration developed. One of these animals, which was killed sixty-eight days after the injection, revealed

4. Kline, B. S.: Experimental Gangrene, *J. Infect. Dis.* **32**:481 (June) 1923.

5. Terrell, E.; Robertson, O., and Coggeshall, L.: Experimental Pneumococcus Lobar Pneumonia in Dog, *J. Clin. Investigation* **12**:393, 1933.

6. Dr. R. S. Stone, of the University of California Hospital, and Dr. Joseph Levitin, associate chief of roentgenology of the Department of Pathology of the Mount Zion Hospital, collaborated in these aspects of the problem.

TABLE 1.—Results of Intrabronchial Injections Into Dogs

Dog No.	Dates of Injection	Temperature		Clinical and Roentgenographic Picture	Pathologic Changes and Comment
		C.	F.		
Series A (Material Removed from Pus Pockets of Patients with Active Pyorrhea, Suspended in a Menstruum of Starch Broth, and Injected into Lower Lobe of Right Lung)					
438	10/ 3/33	38.6	101.5	10/4/33: Dog looked sickly; temperature 40 C. (104 F.); area of density at base of right lung	Dog killed 63 days after injection; autopsy showed an indurated scar in the lower lobe of the right lung, several old adhesions to the pericardium and diaphragm and a healed abscess with scar tissue
	10/ 6/33	40.7	105.2	10/6/33: Area of density at base of right lung with translucent area in middle	
	10/10/33	39.8	103.6	10/9/33: Dyspnea; expectorated brown material; suggestion of abscess or clearing pneumonia	
	10/17/33	38.2	100.7	10/12/33: Abscess cavity larger; small cavity at base of right lung posteriorly	
	10/23/33	38.2	100.7	10/17/33: Infiltration process about cavity clearing	
	10/26/33	39.9	103.8	10/23/33: All clear	
36	3/ 1/34	39.8	103.6	3/2/34: Cough developed, with sputum, lasting 3 weeks; later expectoration became foul and purulent; roentgenogram showed area of increased density at base of right lung	3/26/34: Dog killed; autopsy showed abscess in lower lobe of right lung; purulent bronchitis; atelectasis of rest of lung
	3/19/34	39.0	102.2		
	3/26/34	40.2	104.4	3/6/34: Clear	
32	3/ 1/34	39.2	102.6	2/26/34: Normal	Animal discarded; no autopsy
	3/ 2/34	39.2	102.6	3/2/34: Abscess at base of right lung	
	4/ 7/34	40.4	104.8	3/6/34: Abscess clearing	
	4/ 8/34	39.2	102.6	3/15 to 4/5/34: Clear	
Series B, Controls (Sterile Starch Broth Injected into Lower Lobe of Right Lung)					
470	12/20/33	....	....	1/ 2/34: Bronchoscopy, with negative results	
	1/ 2/34	....	....	1/23/34: Swelling of bronchial mucosa	
	1/25/34	....	....	2/ 8/34: Bronchoscopy, with negative results	
			Roentgenograms: After first injection, an increase in bronchial markings; after later injections, normal		
495	12/20/33	....	....	1/2 to 1/25/34: Bronchoscopy, with negative results	Roentgenograms: First day, normal; seventh to ninth days, increased mottling; after third to fifth injections, normal
	1/ 2/34	....	....	2/8/34: Bronchoscopy, with negative results	
	1/25/34	....	....		

a healed abscess, as shown by the presence of scar tissue. The roentgen evidence during life also suggested pulmonary abscess. A second animal, which was killed twenty-four days after injection, had a pulmonary abscess 2 by 2 cm., purulent bronchitis and atelectasis of the lung. A roentgenogram of the third animal showed evidence of suppuration of the lung, which cleared in thirty days, but autopsy was not performed.

TABLE 2.—Results of Intrabronchial Injection Into Dogs

Dog No.	Date of Injection	Dose of Pus from Guinea-Pigs, Cc.	Dose of Agar (2.5%), Cc.	Roentgenographic Picture	Pathologic Changes
Series C (Single Injection of Pus from Guinea-Pigs Containing a Mixture of Anaerobes into the Lower Lobe of the Right Lung; Bronchus Obstructed by Means of a Plug of Agar)					
348	5/ 3/35	2.0	4	5/9/35: Large area of density at base of right lung posteriorly; abscess (?) 5/10/35: Process at base of lung clearing	5/16/35: Dog killed; autopsy showed pulmonary abscess
341	5/22/35	5.0	5	No roentgenograms taken	5/25/35: Dog died; autopsy showed empyema and pulmonary abscess
347	5/ 3/35	2.0	4	5/6/35: Process in right lung posteriorly suggestive of abscess 5/10/35: Clear 5/20/35: Clear	5/20/35: Dog killed; autopsy showed pneumonia with small area suggestive of pulmonary abscess (?)
355	5/22/35	2.0	4	4/25/35: Normal 5/29/35: Small area of density at base of right lung 5/31/35: Area of increased density at base of right lung 6/ 7/35: Normal	5/6/35: Dog killed; autopsy showed lungs to be normal
241	5/22/35	4.5	5	5/20/35: Normal 5/29/35: Process at base of right lung 5/31/35: Area of increased density at base of right lung posteriorly 6/ 7/35: Normal	6/18/35: Dog killed; results of autopsy negative
249	5/22/35	2.0	5	5/29/35: Area of increased density at base of left lung posteriorly 5/31/35: Area of increased density at base of right lung posteriorly	6/17/35: Dog killed; lungs grossly normal
Series D, Controls (Single Injection of Agar, or of Agar and Heated Pus)					
346	5/29/35	...	5	4/26/35: Normal 5/31/35: Normal 6/ 5/35: Area of increased density	8/7/35: Dog killed; entirely normal
345	5/29/35	...	5	4/26/35: Normal 5/31/35: Atelectasis of lower lobe of right lung 6/5/35: Area of increased density 6/21/35: Inflammation of base of right lung posteriorly	8/6/35: Dog killed; autopsy gave grossly negative results (see histologic report)
356	5/29/35	3.0 (heated)	5	4/26/35: Normal 6/ 5/35: Normal	8/16/35: Dog killed; lungs normal

Table 2 summarizes the data on another group of six dogs which had been given intrabronchial injections of purulent material removed from the inguinal region of guinea-pigs. Two of these dogs, killed three and thirteen days after injection, had large pulmonary abscesses in the infected lobe; pneumonia with small areas of suppuration developed in another and the remaining three dogs were not affected.

In order to control the effects of bronchial obstruction alone, melted agar was introduced intrabronchially into each of two animals. In one of them transient atelectasis developed, while the other remained normal. A third animal, receiving both agar and heated pus, showed no untoward effects. Further details are given under "Summary of Pathologic Changes." Preliminary attempts to produce chronic abscess of the lung by means of pure cultures of anaerobes and aerobes suspended in starch solution were successful only when a pyogenic organism, *Staphylococcus aureus*, was included. The protocols, shown in table 3, give the essential data. It will be noted that freshly isolated strains of *Bact. melaninogenicum* were not markedly pathogenic for the dogs' lung when injected intrabronchially. The roentgenogram of one animal showed an area of increased density in the lobes into which the injections were made. The results were, however, not uniform. The injection of cultures of anaerobic streptococci produced similar results. With repeated intrabronchial injection of this organism, the degree of pulmonary injury, (as judged by the roentgen picture) decreased. When *Bact. melaninogenicum* combined with fusiform bacilli was injected, pneumonitis was observed in two of three animals and pneumonia in the third. Injection of a combination of the three micro-organisms (*Bact. melaninogenicum*, fusiform bacilli and an anaerobic nonhemolytic streptococcus) produced similar results.

When a pyogenic, aerobic micrococcus (a hemolytic strain of *Staph. aureus*) was injected in the usual manner, it was possible, by controlling the size of the dose, to produce pulmonary suppuration in three of five animals.

Control experiments showed that the starch solution which was used for suspending the organisms exerted no appreciable untoward effect on the dogs' lungs when injected intrabronchially.

Observation of daily temperatures revealed no appreciable change in animals in which pulmonary abscess developed. An exception was observed in one animal dying of empyema, complicating pulmonary abscess, in which the temperature rose to 40 C. (104 F.).

White cell counts, made every two or three days after injection, revealed marked leukocytosis, from 28,000 to 38,000 cells per cubic millimeter, in two animals (dogs 347 and 348), in which pulmonary abscess developed. In a third animal (341), in which pulmonary abscess also developed, but which died of empyema two days after injection, the total count reached only 23,000. The other animals (249, 241 and 255), in which no pulmonary lesions developed, showed a less marked leukocytosis. Thus, on the seventh day the counts varied from 11,000 to 15,000; on the fourteenth day, from 13,000 to 19,000, and on the twenty-fourth day, from 16,000 to 34,000 (fig. 1).

Control animals which were given injections of heated pus and agar or agar alone (346, 356 and 345) showed practically no deviation from the normal leukocyte count.

#### SUMMARY OF PATHOLOGIC CHANGES <sup>6a</sup>

Histologic examination confirmed the impression gained on gross examination that although large pulmonary abscesses can be produced in dogs with crude pus which has been passed through a series of guinea-pigs or with material removed from pyorrheal pockets of human beings, a combination of pure cultures of *Bact. melaninogenicum*, fusiform

6a. By Dr. G. R. Biskind and Dr. G. Y. Rusk, Department of Pathology, the Mount Zion Hospital.

TABLE 3.—*Results of Intrabronchial Injection of Various Anaerobic and Aerobic Bacteria Into Dogs\**

Dog No.	Dates of Injection	Temperature	Clinical and Roentgenographic Picture	Pathologic Changes and Comment
			Series E (Bact. melaninogenicum)	
464	10/26/33	40 C. (104 F.) for 24 hrs.; subsided	10/27/33: Area of increased density at base of right lung; animal lost weight 11/ 2/33: Roentgenogram clear	Dog used again in Series H
448	10/26/33	Normal	11/6/33: Increased bronchial markings in lower lobe of right lung	Dog used again in Series H
			Series F (Anaerobic streptococcus)	
467	10/26/33	40.2 C. (104.4 F.)	10/27/33: Area of increased density at base of right lung posteriorly	Discarded
	12/ 8/33	Normal	11/ 3/33: Clear; dog losing weight	
	12/14/33	40.2 C. (104.4 F.)	12/14/33: Small area of density at base of right lung	
	12/21/33	Normal	12/15/33: Clear	
	12/29/33	Normal	12/22/33: Area of density at base of right lung	
	12/29/33	Normal	12/29/33: Clear	Discarded
	12/29/33	Normal	12/30/33: Small area of density at base of right lung	
	12/29/33	Normal	12/30/33: Small area of density at base of right lung	
	12/29/33	Normal	12/30/33: Clear; less reaction with repeated injections	
	12/29/33	Normal	12/30/33: Clear	
466	10/26/33	Normal	10/30/33: Small area of density at base of right lung	Discarded
	12/ 8/33	Normal	11/14/33: Clearing	
	12/14/33	39.6 C. (103.2 F.)	12/22/33: Small area of density at base of right lung	
	12/21/33	Normal	12/29/33: Clear	
	12/29/33	Normal	12/30/33: Normal	
			Series G (Bact. melaninogenicum and fusiform bacilli)	
469	11/10/33	Normal	First injection gave negative results; second produced area of pneumonia in lower lobe of right lung; cleared in 5 days; third injection gave same results as second	Animal was killed 3 days after third injection; autopsy showed induration in lower lobe of right lung and subcardiac lobe (pneumonitis)
	12/15/33	....		
	12/22/33	....		
496	12/22/33	....	First injection produced area of increased density (pneumonitis), which cleared in 10 days; less reaction to second, third and fourth injections	
	1/ 2/34	....	2/8/33: Bronchi slightly reddened; no bronchial plug	
	2/ 1/34	....		Discarded
	2/ 8/34	....		
			Series H (Bact. melaninogenicum and fusiform bacilli)	
500	12/22/33	Normal	12/23/33: Small area of density at base of right lung	Discarded
	1/ 2/34	Normal	12/31/33: Clear	
	2/ 1/34	Normal	1/ 3/34: Pneumonia	
	2/ 8/34	Normal	1/12/34: Clear	
			2/ 2/34: Area of density at base of right lung	
			2/ 7/34: Clear	
			2/ 9/34: Area of density at base of right lung	
			2/20/34: Clear	

Series H (Bact. melaninogenicum, fusiform bacilli and anaerobic streptococci)				
464	11/10/33	40 C. for 3 days	11/13/33: Roentgenogram normal; third injection produced pneumonitis in lower lobe of right lung	Dog killed; autopsy showed mucus plug in lower lobe of right lung; bronchitis and area of consolidation in lower lobe of right lung at periphery (pneumonia); no frank abscess
	12/ 8/33	....	12/23/33: Consolidation in lower lobe of right lung and pleurisy	
	12/15/33	....		
	12/22/33	....		
448	11/10/33	40.5 C. (104.9 F.)	11/14/33: Roentgenogram normal	Autopsy showed area of infiltration of 2.5 sq. cm. posterior surface of lower lobe of right lung (pneumonia); other lung normal
	12/ 8/33	....	12/23/33: Large gray shadow in lower half of lower lobe of right lung	
	12/15/33	....	12/24/33: Animal killed	
	12/22/33	....		
439	11/10/33	Normal	1/2/33: Results of bronchoscopy negative; each injection produced triangular area of pneumonitis; cleared in 6 to 8 days	Discarded
	12/ 8/33	....		
	12/15/33	....		
	12/22/33	....		
449	11/10/33	41.2 C. (106.2 F.)	10/26-12/21/33: Normal	Discarded
	12/ 8/33	....	12/23/33: Small area of increased density	
	12/15/33	....	12/30/33: Cleared at base of right lung	
	12/22/33	....	1/ 3/34: Normal	
Series I (Staphylococcus aureus, hemolytic strain)				
130	5/17/34	....	5/22/34: Cough with purulent sputum; roentgenogram showed abscess in lower lobe of right lung surrounded by pneumonia	Discarded
			5/25/34: Pneumonia clearing; abscess more distinct; no fluid level	
122	5/17/34	....	5/18/34: Died	Autopsy showed bilateral pyothorax; pneumonia of both lungs; pleurisy of lower lobe of right lung
121	5/17/34	....	5/18/34: Died; results similar to those seen in dog 122	Pneumonia and pleurisy
135	7/ 5/34	....	7/15/34: Mucopurulent secretion from lower lobe of right lung	Tip of lower lobe of right lung showed area of induration 3 by 3 cm.; contained yellow necrotic center; smears showed polymorphonuclears and staphylococcus abscesses
			7/20/34: Dog killed	
495	3/16/34	....	3/20/34: Roentgenogram showed abscess cavity	Abscess cavity present in lower lobe of right lung
			3/21/34: Dog killed	

\* Pure cultures were suspended in a menstruum of starch broth and injected into the lower lobe of the right lung.



bacilli and anaerobic streptococci produces only lesions of the pneumonic type. One of the control dogs (345), which was given an injection of agar alone, showed a small area of cellular infiltration and some foreign body giant cells with beginning abscess. Whether or not the agar had become infected spontaneously by micro-organisms normally present in the lung in a manner suggested by Loeffler<sup>7</sup> remains a subject for further investigation.

On several occasions postmortem examination revealed spontaneous healing of pulmonary abscesses. In this respect, too, our data confirmed clinical observations in man. It is noteworthy, moreover, that with the use of the same material a variety of lesions were observed, namely, pneumonia, bronchiectasis and pulmonary abscess. This, as

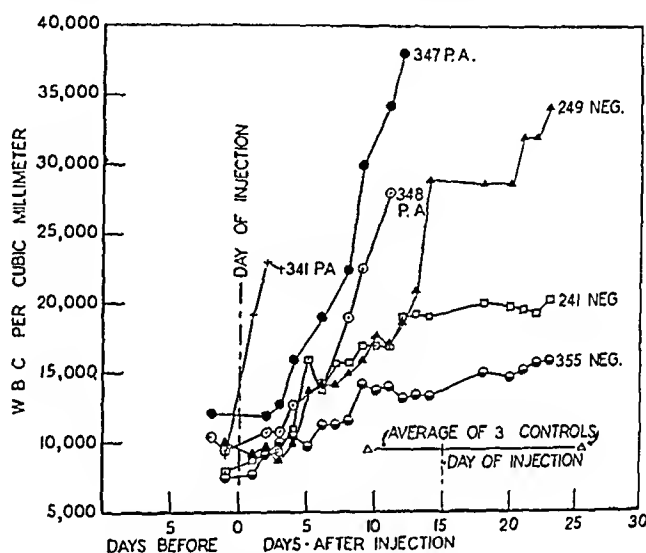


Fig. 1.—Leukocyte count in dogs after intrabronchial injection of pus. P.A. indicates pulmonary abscess.

Smith<sup>3</sup> pointed out, may possibly be referable to variations in the resistance of the host rather than to the bacterial flora. The present investigation also bears out clinical observations to the effect that the roentgenogram cannot always be depended on to aid in the diagnosis of pulmonary abscess. Negative films were frequently reported in animals which showed cavitation post mortem.

A few illustrative histologic protocols will now be cited:

Dog 438 (killed sixty-eight days after injection of pus from pyorrheal pockets of human beings).—The pleura appeared to be above five times its normal thickness. Beneath it there was a chronic inflammatory reaction with lymphocytic, fibroblastic and fibrocytic infiltration. Many foreign body giant cells were in evidence,

7. Loeffler, L.: Experimentelle Lungenabscesse: Beobachtungen ueber Embolie, Deutsche Ztschr. f. Chir. 242:570, 1934.



Fig. 2.—Roentgenogram (lateral view) of the lungs of dog 348, taken during life. The abscess cavity is clearly seen.

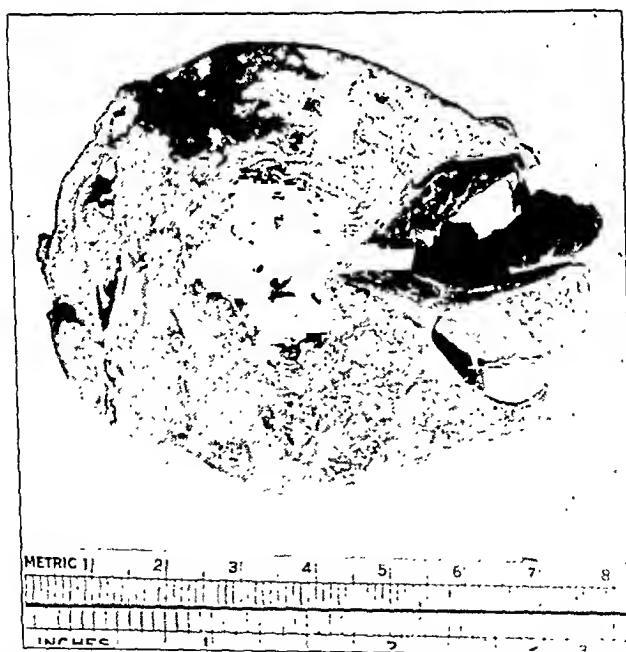


Fig. 3.—A lung of dog 348 removed at necropsy, showing a large abscess cavity produced by the intrabronchial injection of pus from guinea-pigs.

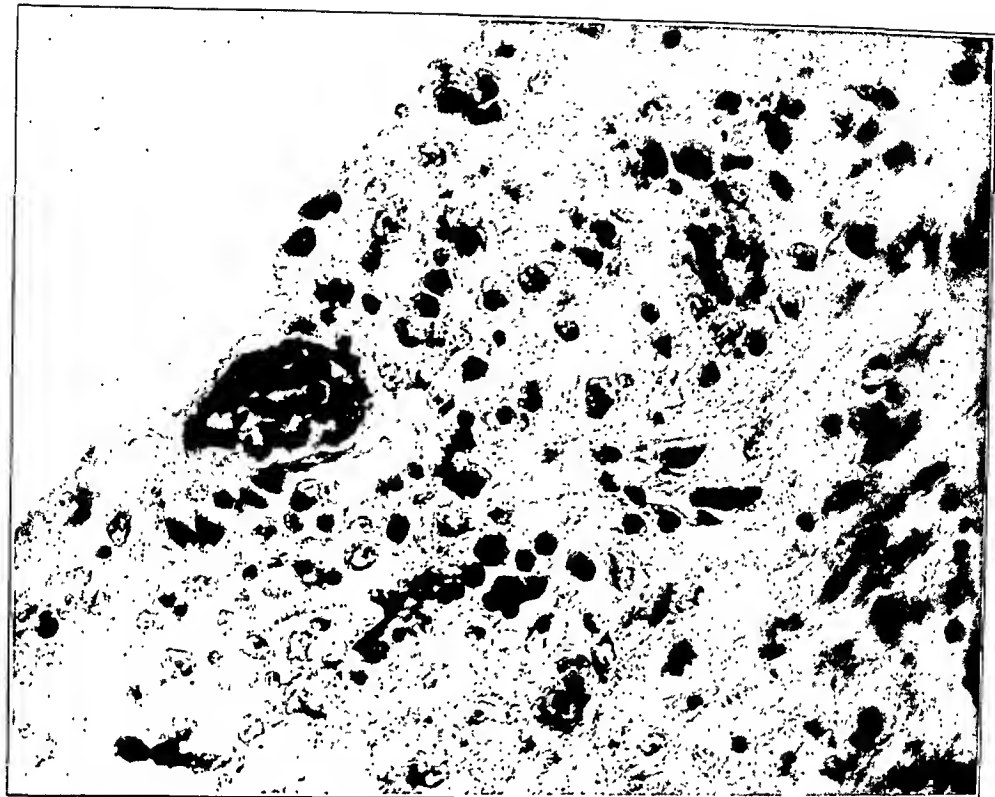


Fig. 4.—Inner layer of the wall of the abscess shown in figure 3.

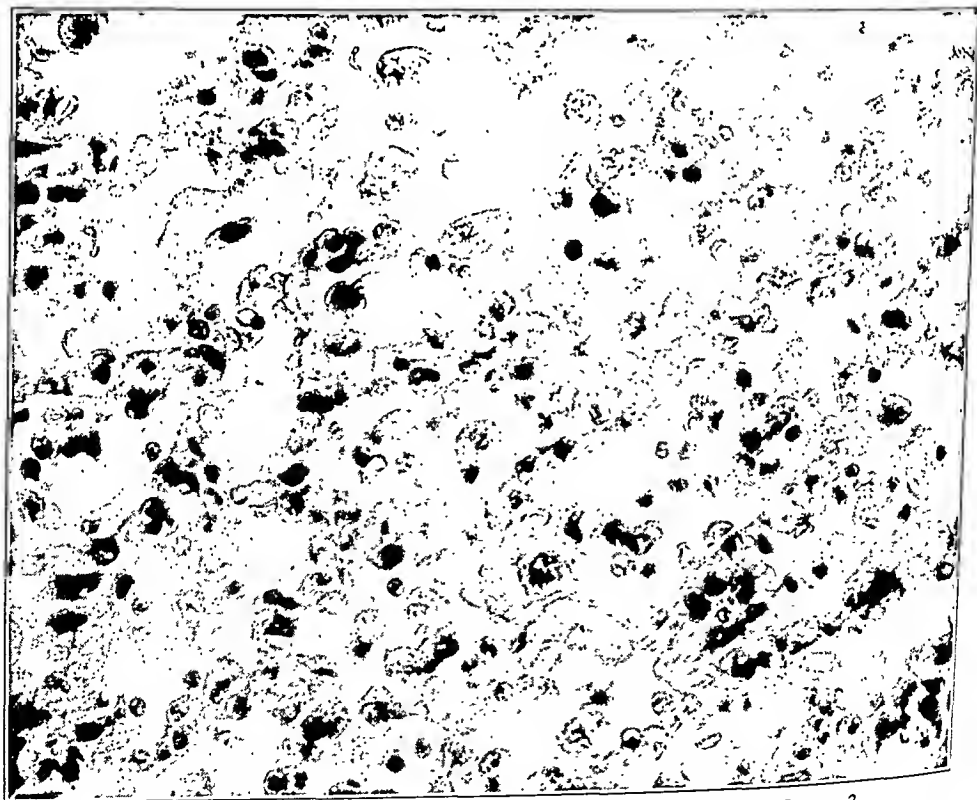


Fig. 5.—Middle layer of the wall of the abscess shown in figure 3.

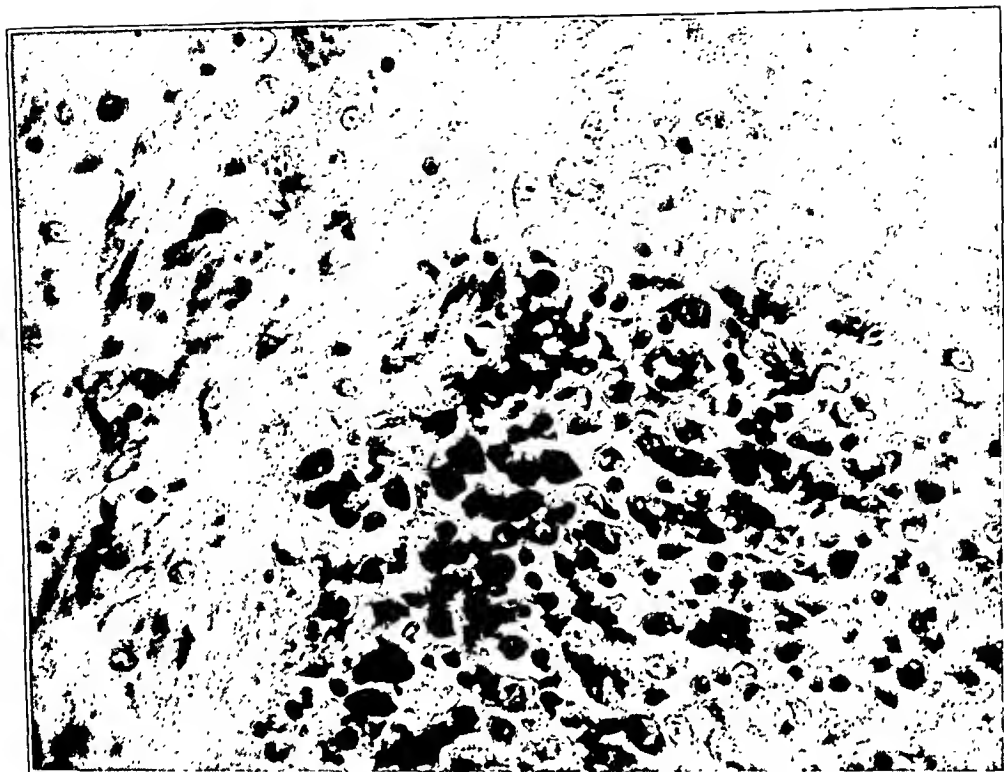


Fig. 6.—Outer layer of the wall of the abscess shown in figure 3.

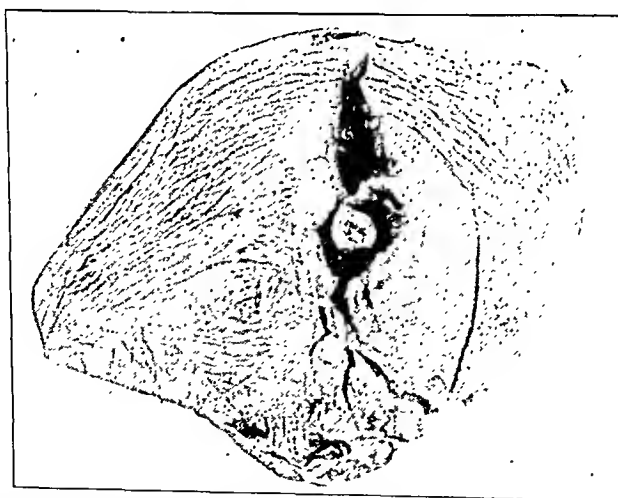


Fig. 7.—Lung of dog 495 with a pulmonary abscess produced by the injection of a hemolytic strain of *Staph. aureus*.

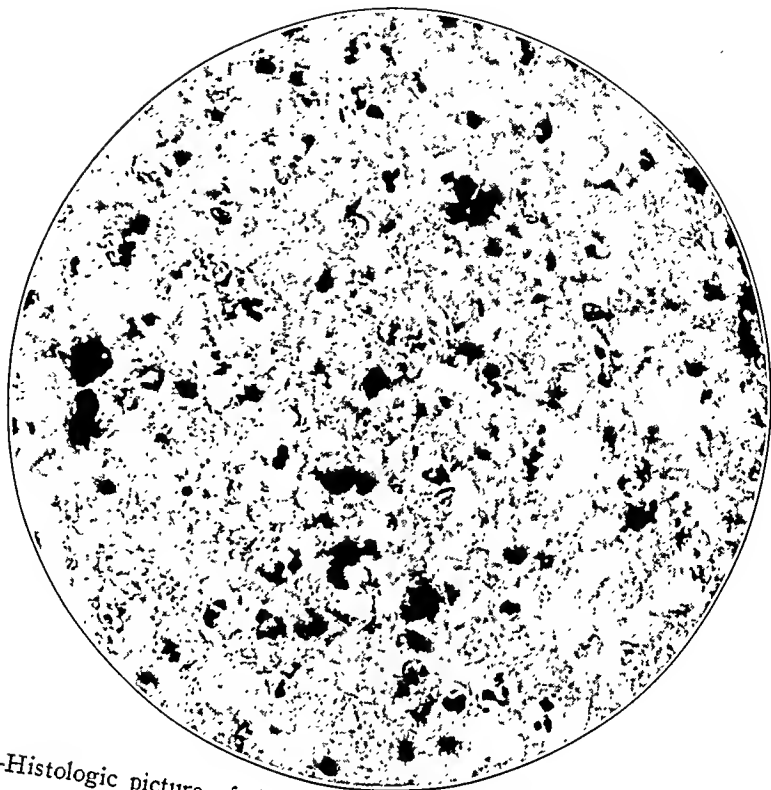


Fig. 8.—Histologic picture of the inner wall of the abscess of dog 495.

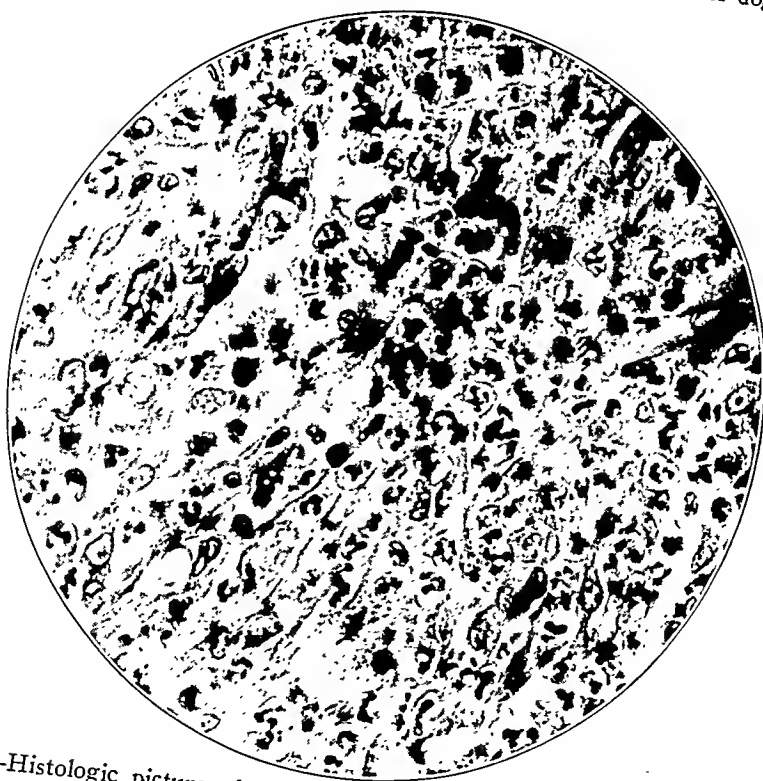


Fig. 9.—Histologic picture of the middle wall of the abscess of dog 495.

and the blood vessels were engorged. There was an occasional area of atelectasis and peribronchial infiltration.

Dog 348 (killed thirteen days after injection of pus from guinea-pigs).—There was an abscess cavity with surrounding inflammatory reaction. The innermost layer contained some red blood cells but consisted mostly of fibroblasts and young blood vessels, the whole resembling granulation tissue. The middle layer consisted of a compact mass of polymorphonuclears, lymphocytes and monocytes. The outermost layer contained cells of the monocytic series and showed destruction of the alveoli.

Dog 469 (killed three days after the third injection of a combination of *Bact. melaninogenicum* and fusiform bacilli).—There were infiltration of the alveoli with

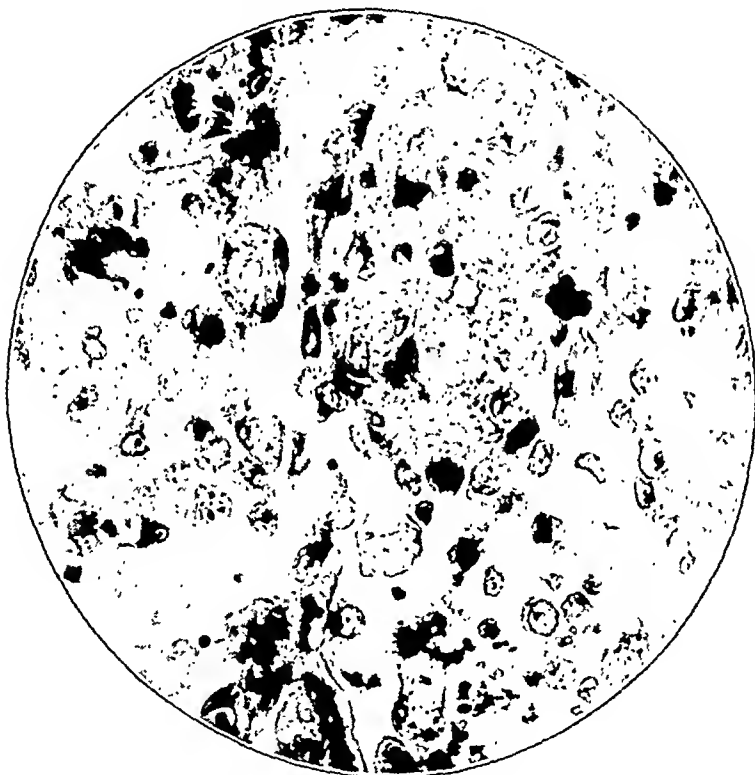


Fig. 10.—Histologic picture of the outer wall of the abscess of dog 495.

polymorphonuclears, red blood cells and fibrin, peribronchial accumulation of polymorphonuclears and moderate congestion of the blood vessels. The picture was that of an acute pneumonic process.

Dog 448 (killed after four injections of a combination of *Bact. melaninogenicum*, fusiform bacilli and an anaerobic streptococcus).—The lungs showed evidence of a subacute inflammatory process. The blood vessels were engorged, and there was a slight hemorrhagic edema of the alveoli with round cell infiltration. There was destruction of the nuclei of the white blood cells. The smaller bronchi were filled with cellular material and showed desquamation of the epithelial layer in some places. The impression was that the condition was an acute pneumonic process.

Dog 464 (killed after four injections, as in the case of dog 448).—The alveoli were filled with white blood cells and edematous fluid. There were occasional

large collections of polymorphonuclears but no evidence of tissue necrosis. The picture was that of bronchopneumonia with areas of hemorrhagic edema.

DOG 495 (killed five days after a single injection of *Staph. aureus-haemolyticus*).—The innermost layer of the wall of the abscess showed extensive necrosis of the cells and numerous clumps of bacteria (gram-positive cocci). Many polymorphonuclear cells were seen near this region; beyond this lay a thick layer of alveolar phagocytes and monocytes. A few foreign body giant cells were also seen. The picture was that of an acute necrotic pneumonitis.

CONTROL DOG 345 (killed about two months after injection of 5 cc. of sterile agar).—Microscopic examination showed an area of infiltration, the cells consisting of polymorphonuclears and monocytes. Around this was an area of collapsed lung parenchyma. There was also evidence of beginning organization. The picture was that of a microscopic area of beginning abscess with interstitial pneumonitis or peribronchial pneumonia.

#### COMMENT

Evidence has been presented that when proper precautions are taken to prevent expulsion of the inoculum from the smaller bronchioles, pulmonary suppuration may be produced in dogs. Similar results have been previously reported by Allen,<sup>8</sup> who employed the difficult technic of isolating and ligating the bronchus after introduction of the infectious material. The positive results with a relatively simple method reported in this communication should be of interest, in view of the many negative findings reported in the literature.<sup>9</sup>

Preliminary work with pure cultures of various anaerobes (*Bact. melaninogenicum*, anaerobic streptococci, fusiform bacilli and a gram-negative motile rod of the *Bacteroides* group) suggests that these organisms alone probably do not cause pulmonary abscess. The variation in results obtained with individual micro-organisms or groups of bacteria may be due to changes in their virulence or to variation in the natural resistance of the animals. Studies now under way in this laboratory are concerned with the pathogenicity of other anaerobes as well as the immunologic defense mechanism of the pulmonary tissues.

#### SUMMARY AND CONCLUSIONS

By means of a technic which prevents the expulsion of the inoculum during coughing and which also causes atelectasis, pulmonary abscesses were produced in several dogs. The infectious material was

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8. Allen, D. S.: Etiology of Abscess of the Lung, *Arch. Surg.* **16**:179 (Jan., pt. 2) 1928.

9. For review of this subject see Maxwell, J.: Lung Abscess, *Quart. J. Med.* **3**:467 (July) 1934. Graham, E. A.; Singer, J. J., and Ballou, H. C.: Surgical Diseases of the Chest, Philadelphia, Lea & Febiger, 1935, p. 709. Marshall, M. S., and Brunn, H.: Bacteriology of Pulmonary Abscess, *Arch. Surg.* **26**:225 (Feb.) 1933. Cutler, E. C.: The Experimental Production of Abscess of the Lung, *Am. J. Dis. Child.* **38**:683 (Oct.) 1929. Crowe, S. J., and Scarff, J. E.: Experimental Abscess of the Lung in the Dog, *Arch. Surg.* **16**:176 (Jan., pt. 2) 1928.

obtained at operation from the lung of a patient with chronic pulmonary abscess and the anaerobes which it contained (*Bact. melaninogenicum*, spirochetes, several types of fusiform bacilli, anaerobic nonhemolytic streptococci, etc.) were kept alive by frequent passage through the inguinal tissues of guinea-pigs, as suggested by Kline<sup>4</sup> and Smith.<sup>5</sup> Another source of material was pus removed from pyorrheal lesions of human beings. The inoculum was introduced directly into a lower lobe bronchus by means of a ureteral catheter and a bronchoscope.

Pure cultures of recently isolated strains of *Bact. melaninogenicum* and anaerobic streptococci were also tested. They did not produce any appreciable pathologic changes in the lungs of dogs. A combination of *Bact. melaninogenicum* and various types of fusiform bacilli caused pneumonitis in two of three animals and pneumonia in a third. The behavior of these micro-organisms under conditions of symbiosis will be investigated further: With a hemolytic strain of *Staph. aureus*, large, acute abscesses of the lung were produced in three of five dogs.

Detailed protocols are given of the roentgenographic picture and pathologic changes in experimental pulmonary abscesses in dogs. Histologic examinations revealed occasional spontaneous healing of the abscesses. Animals in which pulmonary suppuration developed showed marked leukocytosis, the number of cells reaching from 28,000 to 38,000 per cubic millimeter.

The evidence presented suggests that pulmonary abscess may be due in certain cases to aspiration into the lung of infectious material from the upper respiratory passages and the plugging of the corresponding bronchus.

This work was made possible through the interest and clinical cooperation of Dr. Harold Brunn. Miss Dora Gilmore rendered valuable assistance in the bacteriologic studies and Dr. G. Y. Rusk and Dr. G. R. Biskind in the pathologic studies.



# MECHANICAL DECOMPRESSION OF THE INTESTINE IN TREATMENT OF ILEUS

## I. EFFECT OF STRIPPING ON BLOOD PRESSURE

AMBROSE H. STORCK, M.D.

AND

ALTON OCHSNER, M.D.

NEW ORLEANS

The production of immediate and complete relief from distention of the small bowel associated with acute mechanical intestinal obstruction by performing enterostomy and stripping, or milking, the contents of the bowel at the time of operation (fig. 1) would be a desirable accomplishment if the necessary manipulation of the intestine were not accompanied by considerable immediate or delayed undesirable effects. The evaluation of the procedure on the basis of clinical experience has resulted in the expression of widely divergent opinions by observers who have had equal or comparable experience in the management of intestinal obstruction.

Clinicians who have advocated stripping or evacuation of the intestinal contents at the time of operation for the relief of acute intestinal obstruction include Moynihan,<sup>1</sup> Cheever,<sup>2</sup> Holden<sup>3</sup> and Van Zwalenburg.<sup>4</sup> Morton,<sup>5</sup> on the other hand, expressed the opinion of physicians who are opposed to the method and asserted that emptying of a distended loop, even with the slightest manipulation, causes damage to the friable mucosa, hemorrhage and absorption of toxin. He stated:

We think that stripping the bowel is a very dangerous procedure and have evidence that it acts the same in human cases as it does in animals. . . . If one strips the small intestine of a normal animal . . . the carotid blood pressure sinks but . . . in forty-five minutes it returns to its normal. When the

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From the Department of Surgery, the Tulane University of Louisiana School of Medicine.

1. Moynihan, Berkeley: *Abdominal Operations*, ed. 4, Philadelphia, W. B. Saunders Company, 1926, vol. 1.

2. Cheever, David: *Operative Evacuation of the Small Intestine in Paralytic Stasis*, *New England J. Med.* **207**:1125, 1932.

3. Holden, W. B.: *Surgical Treatment of Acute Intestinal Obstruction*, *Surg., Gynec. & Obst.* **50**:184, 1930.

4. Van Zwalenburg, C.: *Hydraulic Vicious Circle as It Develops in the Intestine: Effect of Intraintestinal Pressure on the Pathology and Physiology of the Bowel*, *Am. J. Surg.* **18**:104, 1932.

5. Morton, J. J.: *The Treatment of Ileus as Indicated by Clinical Experience and Experimental Studies*, *Ann. Surg.* **95**:856, 1932.

same thing is done after an ileus of twenty-four hours' duration, the blood pressure [falls] . . . and shows little tendency to return. A proportion of these animals quickly die.

Läwen<sup>6</sup> showed that the trauma incident to the procedure of stripping results in cardiovascular disturbances, including fall in blood pressure. The depressing effect of intestinal stripping on blood pressure is shown by Blalock's<sup>7</sup> investigations on shock, in which he made the following observation:

One of the most frequently used methods of producing shock experimentally consists of traumatizing the intestines. In experiments on twelve dogs, this was



Fig. 1.—Drawing showing the method of evacuating the intestine by stripping.

done by passing the intestines gently between the fingers. This was continued until a sustained low blood pressure resulted. A copious weeping of fluid followed the exposure and handling of the intestines. The fluid had approximately the same composition as the blood plasma. . . . These results indicate that the loss of fluid from and into the traumatized intestines was responsible for the decline in the blood pressure.

It has been the experience of every surgeon that extensive handling of the intra-abdominal viscera produces decrease in blood pressure, and

6. Läwen, A.: Zur Operation des Ileus, *Zentralbl. f. Chir.* 54:1037, 1927.

7. Blalock, Alfred: The Mechanism of the Production and the Treatment of Shock, *J. M. A. Alabama* 1:94 (Sept.) 1931.

frequently surgical shock. Whereas theoretically it is desirable to produce decompression of the intestine in the treatment of ileus as early as possible because of the danger of intramural strangulation, the importance of which has been stressed in previous publications, decompression by enterostomy and intestinal stripping is justified only if the undesirable effects produced by the procedure do not outweigh the beneficial results. In order to evaluate the procedure and to compare the desirable and undesirable effects the present investigation was made. In addition to the changes in blood pressure resulting from intestinal stripping which will be reported in this communication, the effect on subsequent intestinal activity was also determined. These results, reported in the second paper in this series,<sup>8</sup> showed that the motor response of intestine in which obstruction had previously been produced to intravenous administration of twenty times normal lactate-Ringer solution was greater when simple relief from obstruction had been produced than when relief from obstruction was supplemented by stripping.

#### EXPERIMENTAL INVESTIGATION

*Method.*—With the use of ether anesthesia and aseptic technic, complete simple intestinal obstruction was produced in dogs by tying a piece of cotton tape around the terminal portion of the ileum just tight enough to obliterate the lumen of the intestine. The abdomen was closed in layers. The animals, which had had nothing but water for twelve hours prior to this procedure, were given no fluid or food by mouth after the production of obstruction. Fluids, electrolytes and dextrose were supplied by daily infusions of from 400 to 450 cc. of a 5 per cent solution of dextrose in normal lactate-Ringer solution.

At periods varying from twenty-four to seventy-two hours following the production of obstruction, the animals were again anesthetized. At the second operation the animals were prepared so that kymographic tracings could be made showing simultaneously changes in blood pressure, respiratory activity, time intervals and periods during which the intestine was stripped. The changes in blood pressure were recorded by means of a recording mercury manometer connected with a cannula introduced into the common carotid artery on one side, the rubber tubing connecting the manometer with the cannula being filled with a solution of sodium citrate in order to prevent or minimize coagulation of blood in the recording apparatus. The respiratory activity was recorded by a tambour connected with a tracheal tube, through which the anesthetic was administered. Time intervals were indicated by means of a recording watch. Periods during which the intestine was stripped were recorded by a signal magnet equipped with a writing arm. The abdomen was then reopened and a no. 32 Pezzar catheter was introduced through an opening in the terminal portion of the ileum at a level of from 5 to 8 cm. proximal to the side of obstruction. The catheter was held in place by a purse-string suture. Beginning at the upper end of the jejunum, the contents of the entire small intestine distal to this level were evacuated through the enterostomy

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8. Storck, Ambrose H., and Ochsner, Alton: Mechanical Emptying of the Intestinal Contents in Treatment of Ileus: II. Effect on Intestinal Activity, *Arch. Surg.*, this issue, p. 670.

tube by stripping. This was accomplished by drawing the intestine between the index and the middle finger while these fingers were kept in sufficiently close apposition to coapt the walls of the bowel, so that as the intestine was drawn between the fingers the contents would flow into the lower segments of the intestine and finally be discharged through the enterostomy tube. The stripping was performed three times in immediate succession for each observation, for in clinical practice it is usually necessary to strip the intestine several times in order to secure complete evacuation. After completion of the observations the animals were killed by electrocution.

*Results.*—Thirty-two observations were made on five animals, and the effects of stripping on blood pressure reported by Morton <sup>5</sup> and Låwen <sup>6</sup> were corroborated. Three observations were made on an animal in which obstruction had been present for twenty-four hours (fig. 2). In the observations on this animal the greatest fall in blood pressure which occurred after stripping of the entire small intestine was 40 mm. of mercury; the least decrease was 12 mm., and the average decrease was 24.6 mm. The longest period of decrease in blood pressure in this group of observations was ten minutes and the shortest period eight minutes, the average period being nine minutes.

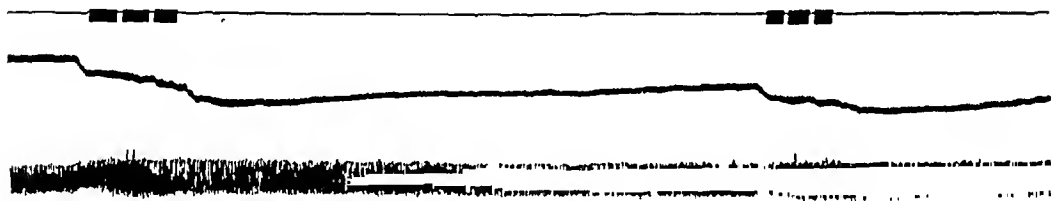


Fig. 2.—Kymographic tracing showing the effect in lowering the blood pressure of stripping the small intestine in which obstruction had been present for twenty-four hours. In this figure and in figures 3 and 4 periods during which the intestine was stripped are indicated by the thick tracings on the line in the upper portion of the figure; the tracing just below shows the changes in blood pressure, and the next tracing, the respiratory activity. The time intervals are recorded in the lower part of the figure.

Thirteen observations were made on two animals which had had intestinal obstruction for forty-eight hours (fig. 3). The greatest fall in blood pressure after stripping in this group of observations was 20 mm. of mercury; the least fall was 4 mm., and the average fall was 12.1 mm. The longest duration of decrease in blood pressure in this group of observations was seventeen minutes; the shortest duration was four minutes, and the average duration was eight and eight-tenths minutes.

Sixteen observations were made on two animals with intestinal obstruction of seventy-two hours' duration (fig. 4). The greatest fall in blood pressure following stripping in this group of observations was 32 mm. of mercury; the least fall was 4 mm., and the average lowering was 15.4 mm. The longest duration of decrease in blood pressure in this group of observations was fifteen and a half minutes; the shortest duration was five minutes, and the average duration was nine and nine-tenths minutes.

The average decrease in blood pressure for all thirty-two observations, i. e., in animals in which obstruction had existed for twenty-four, forty-eight, and seventy-two hours, was 14.9 mm. of mercury, with 40 mm. the greatest decrease and 4 mm. the lowest decrease. The average duration of decrease in blood pressure was nine and four-tenths minutes, the longest duration being seventeen minutes and the shortest four minutes.

In some of the observations, particularly in one group of animals in which obstruction had been present for forty-eight hours, there was progressive fall in blood pressure during the entire experiment, with no considerable return of



Fig. 3.—Kymographic tracing showing the effect in lowering the blood pressure of stripping the small intestine in which obstruction had been present for forty-eight hours.



Fig. 4.—Kymographic tracing showing the effect in lowering the blood pressure of stripping the small intestine in which obstruction had been present for seventy-two hours.

pressure to the level present before stripping was begun. In other instances there was more or less recovery of the blood pressure to the level which preceded the last stripping.

#### COMMENT

As already mentioned, although theoretically the decompression of loops of bowel in relief from intestinal obstruction is desirable in order to prevent intramural strangulation, decompression by intestinal stripping is not justified unless the beneficial results derived from the procedure outweigh the deleterious effects. In investigations

reported in other papers we showed that intestinal activity twenty-four hours after stripping of the intestine was actually less than the intestinal activity in control animals in which stripping had not been performed. The present investigation shows that the procedure is also undesirable because of its depressing effect on blood pressure. A fall in blood pressure following the procedure of stripping was constant and in many instances distinct, regardless of the duration of the obstruction prior to stripping. The duration of decrease in blood pressure varied from four to seventeen minutes and was usually progressively more marked during successive strippings.

Observations on blood pressure in several clinical cases in our experience in which stripping was employed unfortunately could not be satisfactorily or accurately interpreted, because in several instances the patient had received a spinal anesthetic, which may have been responsible for the fall in blood pressure. Our definite impression from clinical observations, however, is that stripping of the small intestine causes distinct lowering of blood pressure, which often necessitates the administration of an infusion during or shortly after the procedure.

#### CONCLUSIONS

Relief from intestinal distention associated with mechanical obstruction by stripping of the intestine has been recommended by some clinicians and condemned by others who have had extensive and comparable experience in the observation and treatment of intestinal obstruction.

The undesirable and considerable degree of lowering of blood pressure that usually accompanies or follows stripping of the small intestine in which obstruction was present has already been observed and reported by others.

In the present experiments we observed that a fall in blood pressure consistently follows stripping.

Because of the serious degree of vascular hypotension which stripping frequently causes and because of the undesirable effect on subsequent motor activity of the intestine and the increased danger of peritonitis incident to the employment of the procedure, we believe that stripping of the intestine is dangerous and should not be performed except when immediate evacuation of the bowel is necessary to permit replacement of the small intestine and closure of the abdominal cavity or to prevent kinks of the "water-hose" type.

# MECHANICAL DECOMPRESSION OF THE INTESTINE IN TREATMENT OF ILEUS

## II. EFFECT OF INTESTINAL ACTIVITY

AMBROSE H. STORCK, M.D.

AND

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NEW ORLEANS

The production of simple relief from block in cases of acute mechanical intestinal obstruction associated with pronounced distention is not followed by evacuation of the fluid and gaseous contents of the distended loops of intestine for at least many hours. For this reason it has occurred to many clinicians that it is sometimes advisable to perform enterostomy and to evacuate the contents of the distended bowel by stripping, or milking, at the time of operation, as illustrated in figure 1 in the first paper in this series. Clinicians who have advocated the procedure expressed the belief that only by this means can the hydraulic vicious circle which develops in association with advanced intestinal obstruction be interrupted. On the other hand, physicians who are opposed to the method believe that more conservative measures are preferable and that the shock, the danger of peritonitis involved in such a procedure and the increase in absorption of toxins through the damaged mucosa which occurs after relief from intramural vascular strangulation make the procedure dangerous and inadvisable.

In his studies on intestinal localization Monks<sup>1</sup> in 1903 demonstrated that almost the entire small intestine could be puckered, or gathered up, on a 1 foot (30 cm.) segment of a rod introduced into the lumen of the intestine. Bottomley<sup>2</sup> credited Monks with the suggestion of the use of a glass tube introduced through an opening in the bowel for the purpose of evacuating the contents of the distended intestine, but he added: "In my own experience the successful employment of this procedure is not very easy." Among clinicians who have advocated treatment for distention and evacuation of the contents of the bowel

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1. Monks, G. H.: Intestinal Localization, *Tr. Am. S. A.* **21**:412, 1903; *Ann. Surg.* **38**:574, 1903.

2. Bottomley, J. T.: Diseases and Injuries of the Jejunum-Ileum and Its Mesentery, in Ochsner, A. J.: *Surgical Diagnosis and Treatment*, Philadelphia, Lea & Febiger, 1921, vol. 3, p. 77.

by means of enterostomy and stripping is Holden,<sup>3</sup> who expressed the belief that the imprisoned intestinal contents above the obstruction should be removed at the time of operation. Van Zwalenburg<sup>4</sup> expressed his conception of the problem and the rational course of action as follows:

Does not the procedure of Holden seem reasonable and encouraging? By gently emptying the bowel he relieves the circulation, restores normal capillary function more promptly, and removes toxic and infective material. Prompt restoration of adequate circulation is the important result. It is obvious that he must avoid trauma. When carefully done there should be little shock from this procedure.

Moynihan<sup>5</sup> expressed his opinion in favor of evacuation of the contents of the distended bowel at the time of operation thus:

No operation for acute obstruction can be considered complete which leaves an intestine, whose function it is to absorb, over-distended by contents of an offensive and poisonous nature. To empty the bowel of its faeculent contents is not to add a danger to the operation by reason of the opening and subsequent suture, but to remove, at the cost of a trifling expenditure of time, that condition which makes most speedily for failure.

Although Moynihan<sup>5</sup> did not advocate stripping, he suggested that evacuation of the bowel should be accomplished by drawing the distended bowel onto a long glass enterostomy tube, a procedure which in practice frequently involves almost as much manipulation of the intestine as does stripping. Cheever<sup>6</sup> strongly advocated stripping and asserted that the importance of immediate relief from distention is so great that he recommended evisceration and evacuation of the contents of the bowel in the treatment of mechanical obstruction and even, in some cases, of ileus associated with peritonitis.

Läwen<sup>7</sup> showed that the procedure of stripping involves trauma which results in cardiovascular disturbance, including fall in blood pressure. We have been able to corroborate these findings in collateral experiments which will be described later. Many clinicians have expressed the belief that the procedure of stripping is inadvisable not only because of the associated shock but because of the damage to the bowel itself. Among the investigators who have condemned the method

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3. Holden, W. B.: *Surgical Treatment of Acute Intestinal Obstruction*, Surg., Gynec. & Obst. **50**:184, 1930.

4. Van Zwalenburg, C.: *Hydraulic Vicious Circle as It Develops in the Intestine: Effect of Intraintestinal Pressure on the Pathology and Physiology of the Bowel*, Am. J. Surg. **18**:104, 1932.

5. Moynihan, Berkeley: *Abdominal Operations*, ed. 4, Philadelphia, W. B. Saunders Company, 1926, vol. 1.

6. Cheever, David: *Operative Evacuation of the Small Intestine in Paralytic Stasis*, New England J. Med. **207**:1125, 1932.

7. Läwen, A.: *Zur Operation des Ileus*, Zentralbl. f. Chir. **54**:1037, 1927



is Morton,<sup>8</sup> who stated that emptying a distended loop of toxic material, even with the slightest manipulation, causes damage to the friable mucosa, hemorrhage and absorption of toxin. He stated:

We think that stripping the bowel is a very dangerous procedure and have evidence that it acts the same in human cases as it does in animals. . . . If one strips the small intestine of a normal animal . . . the carotid blood pressure sinks but recovers again and in forty-five minutes returns to its normal. When the same thing is done after an ileus of twenty-four hours' duration, the blood pressure [falls] . . . and shows little tendency to return. A proportion of these animals quickly die.

Blalock,<sup>9</sup> in discussing the mechanism of the production of shock, stated:

One of the most frequently used methods of producing shock experimentally consists of traumatizing the intestines. In experiments on twelve dogs, this was done by passing the intestines gently between the fingers. This was continued until a sustained low blood pressure resulted. A copious weeping of fluid followed the exposure and handling of the intestines. The fluid had approximately the same composition as the blood plasma. . . . These results indicate that the loss of fluid from and into the traumatized intestine was responsible for the decline in the blood pressure.

The alterations in intestinal motility occurring in association with acute obstruction of the small intestine, as has been shown by Henderson,<sup>10</sup> Van Zwalenburg,<sup>4</sup> Van Beuren<sup>11</sup> and others, are intimately related to, or dependent on, distention of the intestines. In acute mechanical obstruction a vicious circle is quickly produced by the following means: As a result of the mechanical block the gas and fluid normally contained within the intestine accumulate, and distention of the bowel occurs. As a result of the intestinal distention there occur increased secretion into and decreased absorption from the intestine. When the intra-intestinal pressure and distention of the bowel become marked, as was first emphasized by Van Zwalenburg,<sup>4</sup> the vessels within the wall of the intestine become stretched and compressed, resulting in interference with the blood supply. Dragstedt, Lang and Millet<sup>12</sup> showed

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8. Morton, J. J.: The Treatment of Ileus as Indicated by Clinical Experience and Experimental Studies, *Ann. Surg.* **95**:856, 1932.

9. Blalock, Alfred: The Mechanism of the Production and the Treatment of Shock, *J. M. A. Alabama* **1**:94 (Sept.) 1931.

10. Henderson, V. E.: Studies in Peristaltic Fatigue, *Am. J. Physiol.* **66**:380, 1923.

11. Van Beuren, F. T., Jr.: Enterostomy in Acute Ileus—the Time Element: A Preliminary Report, *Am. J. Surg.* **1**:285, 1926.

12. Dragstedt, C. A.; Lang, V. F., and Millet, R. F.: The Relative Effects of Distention on Different Portions of the Intestine, *Arch. Surg.* **18**:2257 (June) 1929.

that there is considerable variation in the intramural blood supply of various parts of the intestine and that owing to this anatomic variation pressure within the bowel exerts varying influences on the blood supply, as is shown in figure 1. The interference with blood flow is greatest in the duodenum, where the vasa recta for much of their extent are situated internal to the muscular layers and can readily be compressed by increased intra-intestinal pressure, and is least in the colon, where the vasa recta for a greater portion of their extent lie external to the muscular coats and are less susceptible to compression by intra-intestinal pressure.

Kocher<sup>13</sup> in 1899 showed that pressure of gas within the lumen of the intestine may interfere with circulation and cause gangrene of the wall of the bowel. Van Zwalenburg<sup>14</sup> in 1907 made observations on

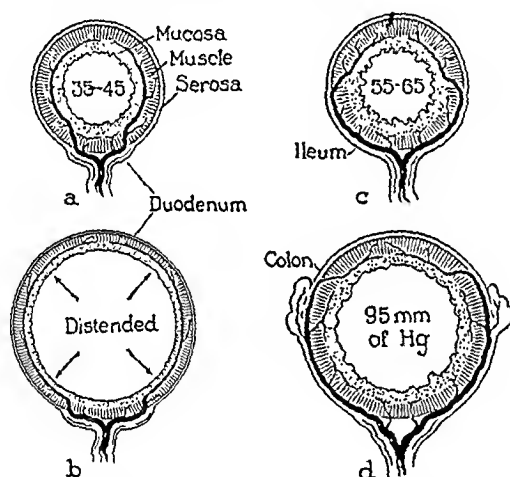


Fig. 1.—Diagrammatic representation of the variations in the points of entrance of blood vessels into the intestinal wall (*a*, *c* and *d*), based on the observations of Dragstedt, Lang and Millet<sup>12</sup> and Morton.<sup>8</sup> Narrowing and compression of the blood vessels occur when the intestine becomes distended, as shown in the illustration (*b*). Less intra-intestinal pressure is required to cause intramural vascular strangulation in the duodenum because the duodenal vessels pierce the muscular coats near the mesenteric border and throughout almost their entire length are subjected to compression by the muscularis. Much greater intra-intestinal pressure is required to cause intramural strangulation in the colon, the vasa recta of which do not pierce the muscularis until they reach nearly the antimesenteric border.

the effect of varying intra-intestinal pressures on the blood flow in the wall of the bowel. He found that at a pressure of 30 mm. of mercury

13. Kocher, T.: Ueber Ileus, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 4:195. 1899; cited by Gatch, Trusler and Ayers.<sup>15</sup>

14. Van Zwalenburg, C. A.: Strangulation Resulting from Distention of Hollow Viscera, Ann. Surg. 46:780, 1907.

some capillary streams were arrested, at a pressure of 60 mm. the current was arrested in small veins and slowed in most of the veins, at a pressure of 90 mm. all the blood streams moved slowly and many currents changed direction frequently and at a pressure of 130 mm. there was oscillation of corpuscles but all circulation had ceased.

He came to the following conclusions at that time:

The demonstration seems complete that distention of the gut (or of other hollow viscera) interferes with the circulation in its wall and allows infiltration and effusion to take place into its wall and lumen and any other open spaces which may come within its influence. The return circulation is retarded at comparatively slight pressures. Effusion follows, as in all obstructions to venous flow. As the average venous pressure in the intestine under ordinary circumstances probably varies from 4 to 10 mm. of mercury, any pressure beyond that will offer some resistance to the return current.

Gatch, Trusler and Ayers<sup>15</sup> studied intestinal distention in relation to circulation in the bowel by recording the effect of this distention on the rate of blood flow in the veins. They showed that the blood flow through the wall of the bowel decreases as the distention increases and that it ceases when the pressure within the bowel equals the systolic blood pressure. Burget, Martzloff, Suckow and Thornton<sup>16</sup> formed a subcutaneous closed intestinal loop with an intact mesentery. After varying periods the pressure within the loop was determined and was decreased by aspirating the contents. Various portions of the intestine were used for the production of the loop. It was found that the amount of pressure in the closed loops varied from 0 to 36 cm. of water. The high pressures recorded within the first few days following operation were considered to be capable of arresting intramural circulation. A loop markedly distended by a pressure of from 25 to 30 mm. of mercury had its circulation practically blocked. This was evidenced by necrosis in the antimesenteric border of the loop. The average high pressure was 39.5 cm. of water. The clinical manifestations in the dogs in this series were not marked when the pressure was low, but the animals did not appear to be lively and refused food if the loop was distended.

Krogh<sup>17</sup> stated that when stasis occurs, even in spite of free venous outflow, filtration of plasma is rapid, and Müller<sup>18</sup> expressed the opinion

15. Gatch, W. D.; Trusler, H. W., and Ayers, K. D.: *The Effects of Gaseous Distention on Obstructed Bowel: Incarceration of Intestines by Gas Traps*, *Arch. Surg.* **14**:1215 (June) 1927.

16. Burget, G. Z.; Martzloff, K.; Suckow, G., and Thornton, R. C. B.: *The Closed Intestinal Loop: I. Relation of Intraloop (Jejunum) Pressure to the Clinical Condition of the Animal*, *Arch. Surg.* **21**:829 (Nov.) 1930.

17. Krogh, A.: *Anatomy and Physiology of Capillaries*, New Haven, Conn., Yale University Press, 1929, p. 315.

18. Müller, E. F.: *Ueber den paralytischen Ileus*, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **41**:417, 1929.

that hyperemia of the intestinal wall in the early stage of obstruction results in increased intestinal secretion. Owings and his associates<sup>19</sup> observed that the pressure after twenty-four hours in isolated duodeno-jejunal loops was 50 cm. of water. Morton<sup>8</sup> found that, whereas the normal intra-intestinal pressure varies from 2 to 4 cm. of water, after obstruction had been present for twenty-four hours the pressure within the duodenum and the ileum had increased from 28 to 36 cm. and from 4.5 to 5 cm., respectively. The reason for the relatively greater increase in the intraduodenal pressure is that the function of the duodenum is largely secretory whereas that of the ileum is principally absorptive. Morton<sup>8</sup> found that the duodenum secretes from five to ten times as much fluid as the ileum in a given period. As a result of this activity and also because of the presence of the biliary and pancreatic secretions in the upper portion of the intestine, the intra-intestinal pressure within the duodenum and the upper portion of the jejunum is much greater than that in the ileum. Herrin and Meek<sup>20</sup> studied the effect of distention in dogs with varying types of fistulas. On distending the intestines by means of a balloon inflated to a pressure of from 80 to 90 mm. of mercury, they noted a marked increase in the secretion from the fistulas. As much as 500 cc. of fluid was formed in a fistula 20 cm. long during the course of twenty-four hours. They stated that "distention is a strong stimulus to intestinal secretion and in obstruction this must work in a vicious circle." Raine and Perry<sup>21</sup> concluded that diminishing intra-intestinal pressure in an obstructed bowel prolongs the life of rabbits because it diminishes secretion and promotes reabsorption.

Henderson,<sup>10</sup> using sections of the intestine of the guinea-pig placed in Ringer's solution, found that responses in the form of peristaltic movements occurred with increases in pressure of from 15 to 25 mm. of water. If the pressure was maintained failure of these peristaltic movements occurred sooner or later. If when the movements ceased the pressure was lowered, the intestine, after a period of rest, again responded on increasing the pressure to the point which stimulated peristalsis. However, if pressure was maintained peristaltic failure was absolute in some cases, or if movements were present they tended to

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19. Owings, J. C.; McIntosh, O. A.; Stone, H. B., and Weinberg, J. A.: Intra-Intestinal Pressure in Obstruction, *Arch. Surg.* **17**:507 (Sept.) 1928.

20. Herrin, R. C., and Meek, W. J.: Studies on Intestinal Obstruction, *Am. J. Physiol.* **97**:532, 1931.

21. Raine, F., and Perry, M. C.: Intestinal Obstruction: Experimental Studies on Toxicity, Intra-Intestinal Pressure and Chloride Therapy, *Arch. Surg.* **19**:478 (Sept.) 1929.

become shorter and to occur at longer intervals, and irregularities in the movements often appeared. In his conclusions Henderson<sup>10</sup> stated:

Peristaltic failure is not due to a failure of the activity of the musculature alone as there is evidence which suggests that some, in part at least, is due to fatigue of the nerve net.

Hotz,<sup>22</sup> using rabbits, opened a loop of bowel and replaced it in the abdomen. Twenty-four hours later, after peritonitis had developed, with the animal under anesthesia the loop of bowel was withdrawn from the abdominal cavity and placed in a bath of salt solution. Careful observations concerning the activity of the loop showed that the muscle of a loop treated in this way continued to contract rhythmically even when peritonitis was so severe that the serous coat was covered with a thick layer of pus. Rhythmic contractions ceased only after the bowel had for several hours been distended with gas. Hotz<sup>22</sup> concluded, therefore, that injury to the muscle in peritonitis is due not to toxins but to distention by gas. The gas accumulates when absorption is impaired. Alvarez and Hosoi,<sup>23</sup> in discussing the effects of distention, referred to the observation of Usadel,<sup>24</sup> who showed that distention of the intestine compresses not only the arterioles that bring necessary blood to the muscle but the venules of the portal system, which normally carry the gas away as fast as it is formed. They concluded that once gaseous distention and muscular paralysis appear they are likely to become progressively worse through the formation of a vicious circle.

Hartwell, Hoguet and Beeckman<sup>25</sup> and Murphy and Brooks<sup>26</sup> emphasized that toxic materials are not readily absorbed by the normal mucosa. Stone<sup>27</sup> discussed the selective absorptive power of normal mucosa and referred to the not infrequent occurrence of death, apparently due to toxemia, occurring soon after relief of an obstruction which had existed for sufficient time to cause considerable distention. He expressed the belief that, since it has been shown that toxic material

22. Hotz, G.: Beiträge zur Pathologie der Darmbewegungen, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **20**:257, 1909.

23. Alvarez, W. C., and Hosoi, K.: What Has Happened to the Unobstructed Bowel That Fails to Transport Fluids and Gas? Am. J. Surg. **6**:569, 1929.

24. Usadel, W.: Die Kreislaufstörung bei der freien eitrigen Bauchfellentzündung und der Einfluss der Darmbewegung auf den Pfortaderkreislauf, Arch. f. klin. Chir. **142**:423, 1926.

25. Hartwell, J. A.; Hoguet, J. P., and Beeckman, F.: An Experimental Study of Intestinal Obstruction, Arch. Int. Med. **13**:701 (May) 1914.

26. Murphy, F. T., and Brooks, B.: Intestinal Obstruction: An Experimental Study of the Causes of Symptoms and Death, Arch. Int. Med. **15**:392 (March) 1915.

27. Stone, H. B.: The Clinical Application of Experimental Studies in Intestinal Obstruction, Am. J. Surg. **1**:282, 1926.

entering the empty, collapsed normal bowel below the obstruction is not absorbed there, the mechanism under such circumstances is as follows: The production of relief of the obstruction and the consequent fall in intra-intestinal pressure may permit rapid return of circulation through the wall of the bowel, which may carry into the general circulation poisonous material that has entered the wall of the intestine during the period when it was distended. According to his explanation, he apparently assumed that transperitoneal absorption, presumably occurring during distention, is of less overwhelming nature than absorption via the mesenteric blood and lymph vessels after the distention is relieved. Dragstedt, Dragstedt, McClintock and Chase<sup>28</sup> concluded that injury to the mucosa of the intestine, particularly that resulting from disturbance of the blood supply to the intestine, greatly facilitates the absorption of poisons. The factor of distention in short closed intestinal loops is of paramount importance in the production of the toxemia, since if the distention is prevented toxemia does not occur in the majority of cases. Dragstedt<sup>29</sup> stated that the toxemia and the decrease in concentration of blood chlorides are dependent on distention of the closed intestinal segment. If this distention is relieved by aspiration of the fluid within the segment toxemia is relieved, and there occurs a proportionate return in the concentration of blood chlorides toward the normal level. Stone and Firor,<sup>30</sup> commenting on a group of experiments concerning the effect of distention on absorption due to obstruction of the bowel, pointed out that india ink, like the toxins from obstructed loops, is not absorbed when injected into the lumen of the normal bowel, that it is not absorbed when the lumen is narrow and kinked but is still patent but that it is absorbed when complete obstruction exists for even such a short period that the animal does not succumb to the obstruction. In another series of experiments living excised loops of the lower portion of the duodenum and the upper part of the jejunum obtained from dogs were suspended in flasks of Ringer's solution. Observations were made concerning the toxicity of the solution in which the loops were suspended, and the findings indicated that toxin does not pass through a suspended living loop of bowel without some increase in intra-intestinal pressure. Gatch<sup>31</sup> showed experimentally that, while

28. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: A Study of the Factors Involved in the Production and Absorption of Toxic Materials from the Intestine, *J. Exper. Med.* **30**:109, 1919.

29. Dragstedt, L. R.: Blood Chemistry in Intestinal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **25**:239, 1928.

30. Stone, H. B., and Firor, W. M.: Absorption in Intestinal Obstruction: Intra-Intestinal Pressure as a Factor, *Tr. South. S. A.* **37**:173, 1924.

31. Gatch, W. D.: The Blood Chemistry, Toxemia, and Mechanism of Advanced Intestinal Obstruction with Deductions on Treatment, *Illinois M. J.* **60**:236, 1931.

distention of the bowel prevents or diminishes direct absorption into the blood stream, it proportionately increases absorption by way of the peritoneum, because effusion can take place more readily through a thin and damaged intestinal wall than through a wall which is not injured and is of normal thickness. He further stated that absorption decreases as circulation through the bowel decreases until, with the onset of gangrene, all absorption must be transperitoneal. Since observers are agreed that the toxins from an obstructed bowel are slowly absorbed through intact mucosa and since injury of the mucosa does not occur until a rather high degree of distention has been reached, which would interfere with the circulation of the intestinal wall, it follows that the chief route of absorption must be transperitoneal and that the chief absorption of toxins in intestinal obstruction occurs rather late in the course of the disease, after well marked distention of the bowel has occurred. Van Beuren<sup>33</sup> studied the pathologic changes occurring in distended loops of bowel and observed that the characteristic feature was areas of hemorrhagic infarction on the antimesenteric surface of the intestine, varying from simple infarction to perforation, depending on the duration of the distention. The mechanism of this infarction appears to be as follows: Distention of the intestine increases its diameter. Any increase in its diameter is tripled by the increase in its circumference. In other words, if the diameter of the intestine is increased from 1 to 3 cm. by distention its circumference is at the same time increased from 3 to 9 cm. Thus, the difference in the diameter is only 2 cm. whereas the difference in circumference is 6 cm. A moderate increase in diameter therefore results in considerable stretching of the wall. The intestinal vessels pass between the layers of the wall along its circumference from their origin at the mesenteric border to their terminal anastomoses at the antimesenteric surface, the walls becoming progressively thinner and the lumen narrower. Because the vessels are elastic, the stretching of the intestinal wall due to distention still further thins the wall of the vessel and narrows the lumen, an effect similar to that produced by stretching a rubber tube. At the same time the pressure from within the intestine tends to flatten the lumen of the vessel. The thinning of the vascular wall is maximal at the antimesenteric surface of the intestine where the terminal anastomoses occur, and the intra-intestinal pressure being uniform throughout the lumen of the intestine, the maximum effect occurs at the antimesenteric surface, where the combination of the factors—the pressure, the thin wall and the narrow lumen—finally results in obliteration of the vessel. This obliteration occurs sooner

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32. Footnote deleted by author.

33. Van Beuren, F. T.: *The Mechanism of Intestinal Perforation Due to Distention*, *Ann. Surg.* **83**:69, 1926.

in the vein than in the artery on account of the lessened resistance of the wall and the lower venous pressure. The blood continues to flow through the arteries until the pressure against the obliterated vein suffices to rupture the wall of the vessel and permit extravasation and coagulation. Finally, the artery as well as the vein is occluded. The area of tissue supplied by these terminal vessels is thus deprived of circulation, and necrosis occurs. This necrosis is usually first evident in the submucosa and inner muscular coat but rapidly extends to the other coats of the intestinal wall, and perforation may occur within twenty-four hours after the discoloration due to the hemorrhagic infarct was first noticed. Hofmann<sup>34</sup> expressed agreement with Van Beuren<sup>33</sup> in regard to the effect of distention of the bowel on the blood supply to the intestinal wall and stated that in addition to the overfilling of the vessels marked edema, especially of the submucosa and tunica propria, occurs. He observed the circular muscle fibers to be edematous, whereas the longitudinal muscles and serosa were scarcely affected. Transudation occurred into the lumen of the intestine. In cases of long-standing involvement, there resulted hemorrhagic infarcts, especially in the submucosa, and the intestinal wall became friable. Hematoma was likely to result. Occasional thrombosis of the submucous veins could be noted. The changes in the intestinal wall were dependent on the amount of distention. Necrosis at times was followed by ulceration.

In this review of the literature it is evident that distention plays an important part in interfering with intestinal motility by the following means: (1) in the early stages it causes fatigue through stretching of the muscles; (2) in the intermediate stages it causes interference with the blood supply to the muscles, with resulting anoxemia of the bowel, and (3) in the terminal stage it causes actual necrosis of the musculature.

When intra-intestinal pressure is of such degree or duration that the intestinal musculature is damaged or the activity of the intestine interfered with, the vicious circle of which this is a result must be interrupted in order that viability of the intestinal musculature may be maintained. This imperative relief from distention may be accomplished by simple enterostomy or by mechanical evacuation of the contents of the bowel by stripping, after formation of an enterostomy opening. Obviously, intestinal distention, with its detrimental effects on the intestinal vascularity and activity, must be relieved, and theoretically any procedure which accomplishes this should be desirable. It would seem therefore that the procedure of intestinal stripping in the treatment of acute intestinal obstruction would be not only permissible but desirable. The variations in such factors as the site and the dura-

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34. Hofmann, M.: *Das Verhalten des Darmes bei Incarceration, insbesondere an den Schnürfurchen*, Beitr. z. klin. Chir. **54**:85, 1907.



tion of the obstruction encountered in clinical experience make it difficult to evaluate the procedure of stripping on the basis of observations made on man. We have employed the procedure in sixteen clinical cases of ileus associated with pronounced distention, but because of the many variables present in these cases it is difficult to draw any definite conclusions concerning the value of stripping on the basis of the observations. Because of the inconclusive results obtained in the clinical cases in our series and the conflicting clinical reports an attempt was made to evaluate the results of stripping of the distended loops of bowel in experimentally produced ileus. Whereas L  wen<sup>7</sup> and Morton<sup>8</sup> had previously shown that stripping of the distended intestine causes a fall in blood pressure during and immediately after the manipulation, no one had demonstrated either clinically or experimentally what happens to the intestine after the stripping. Theoretically, aside from the trauma, the activity of the intestine should be greater after the emptying of the distended loops, since the intramural blood supply should be better.

In order to determine the relative values of simple relief and relief by intestinal stripping in the treatment of ileus, the present investigation was undertaken. It is concerned with observations on intestinal activity twenty-four hours after the production of simple relief and relief supplemented by intestinal stripping in instances of mechanical obstruction. The observations were made on animals with low simple obstruction, as it is for this type that the procedure of stripping has been most frequently advocated and applied. Dogs were used, and mechanical obstruction of the lower portion of the ileum was produced. In one group of experiments the effect of stripping of the bowel on blood pressure was determined, and in another group the motor activity of the bowel was studied twenty-four hours after the relief of the obstruction. Our observations on the effect of stripping on blood pressure are reported in detail in the first paper in this series, but one of the kymographic tracings showing the effect of stripping in the lowering of blood pressure is shown in figure 2 of that paper.

In one group of experiments in which the motor activity of the dog's intestine was studied twenty-four hours after relief of complete simple intestinal obstruction, only simple relief of the obstruction was produced, while in another group, in addition to relief of the obstruction, the contents of the entire small bowel were evacuated and distention was immediately relieved by performing an enterostomy and stripping out the fluid and gaseous contents above the site of obstruction. Observations in both groups were made on animals in which the obstruction had existed for periods varying from forty-eight to one hundred and forty-four hours.

## EXPERIMENTAL INVESTIGATION

*Methods.*—With the use of ether anesthesia and aseptic technic, complete simple intestinal obstruction was produced in dogs by tying a piece of cotton tape around the terminal portion of the ileum just tight enough to obliterate the lumen of the intestine. The abdomen was then closed in layers. The animals, which had had nothing but water for twelve hours prior to this procedure, were given no fluid or food by mouth after the production of obstruction. Fluids, electrolytes and dextrose were supplied by daily infusions of from 400 to 450 cc. of a 5 per cent solution of dextrose in normal lactate-Ringer solution.

At periods varying from forty-eight to one hundred and forty-four hours after the production of obstruction the animals were again anesthetized and the abdomen reopened. At this second operation simple relief of the obstruction was produced in one group of animals by merely untying and removing the constricting tape, after which the abdomen was closed. In the other group, before the obstructing tape was removed, a no. 32 Pezza catheter was introduced through an opening in the terminal portion of the ileum at a level of from 5 to 8 cm. proximal to the site of obstruction. The catheter was held in place and leakage prevented by means of a purse-string suture. The entire small intestine was then eviscerated, and the loops were surrounded with gauze sponges saturated with warm physiologic solution of sodium chloride. Beginning at the upper end of the jejunum, the contents of the entire small intestine distal to this level were evacuated through the enterostomy tube by stripping. This was accomplished by drawing the intestine between the index and middle fingers while these fingers were kept in sufficiently close apposition to coapt the walls of the bowel, so that as the intestine was drawn between the fingers the contents would flow into the lower segments of the small intestine and finally be discharged through the enterostomy tube. After completion of the stripping the enterostomy tube was removed, care being taken to avoid spillage and peritoneal contamination. The opening in the intestine was closed; the constricting tape was removed, and the abdominal wall was reclosed.

Twenty-four hours after the procedures just described, i. e., production of simple relief of obstruction or production of relief of obstruction and stripping of the intestine, the animals were again anesthetized and prepared so that kymographic tracings could be made showing simultaneously changes in blood pressure, respiratory activity and intestinal activity, according to the technic described by Ochsner, Gage and Cutting.<sup>35</sup> The changes in blood pressure were recorded by means of a recording mercury manometer connected with a cannula introduced into the common carotid artery on one side, the rubber tubing connecting the manometer with the cannula being filled with a solution of sodium citrate in order to prevent or minimize coagulation of blood in the recording apparatus. The intestinal activity was recorded by means of a Maury tambour connected with a thin rubber balloon introduced into the lumen of the ileum.

Observations were made after the injection into the external jugular vein of uniform amounts (10 cc.) of lactate-Ringer solution of twenty times the normal concentration. The effective peristalsis-stimulating property of this solution has been demonstrated and described by Ochsner, Gage and Cutting<sup>35</sup> in their studies concerning the effect of hypertonic salt solutions on intestinal motility in obstruction of the intestine.

35. Ochsner, Alton; Gage, I. M., and Cutting, R. A.: Influence of Hypertonic Salt Solutions on the Motility of Normal and of Obstructed Intestine: An Experimental Study, *Arch. Surg.* 27:742 (Oct.) 1933.

Sixty-nine animals were used in these experiments. Five animals were used for observations on the effect of intestinal stripping on blood pressure. Twenty-eight animals died before observations on intestinal motility could be made. In most instances death was due to peritonitis resulting from rupture of the intestine, and occurred in animals in which obstruction had been present for seventy-two hours or longer. Several animals died of pneumonitis. Two were killed after one hundred and forty-four hours and were not used because of the slight degree of intestinal distention. The observations made on one animal were not included because of a persistent leak in the recording apparatus. Thirty-three animals were used in making observations concerning intestinal motility. Forty-six observations were made on fifteen animals in which simple relief of the obstruction was effected. Sixty-two observations were made on eighteen animals in which both relief of the obstruction and stripping were effected.

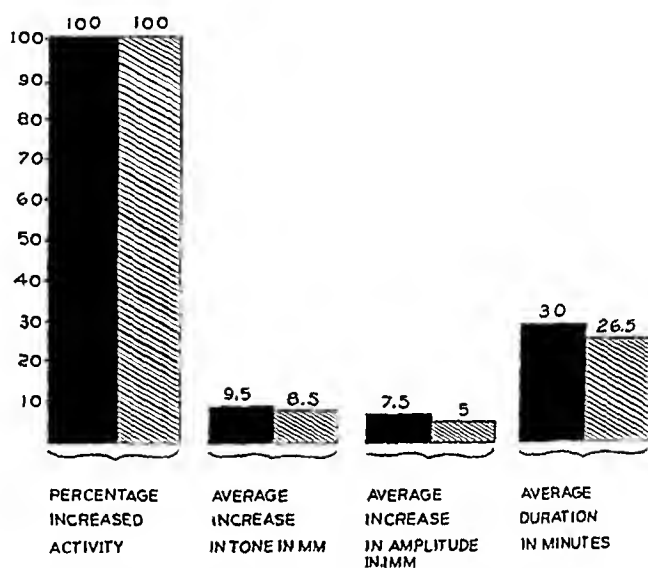


Fig. 2.—Graphic representation of intestinal activity twenty-four hours after relief of intestinal obstruction which had existed for forty-eight hours. Both in the animals in which simple relief was produced (two observations) and in the animals in which relief of obstruction was obtained by stripping (two observations), there was an increase in activity following the intravenous administration of 10 cc. of twenty times normal lactate-Ringer solution in 100 per cent of the animals. In this chart and in the charts in figures 5, 8, 11 and 14 the values for the animals in which simple relief was produced are indicated by black areas and those for the animals in which relief from obstruction was produced and stripping done by areas of cross-hatching. The average increase in tone for the two groups was 9.5 and 8.5 mm., respectively; the average increase in amplitude, 0.75 and 0.5 mm., respectively, and the average duration of the increase in activity, 30 and 26.5 minutes, respectively.

*Results.*—In the group of experiments in which observations were made concerning the effect of stripping on blood pressure, the observations of Låwen<sup>7</sup> and Morton<sup>8</sup> were corroborated. Ten observations were made on two animals, and a fall in blood pressure consistently

occurred after stripping. We have observed this hypotension in clinical cases during or after stripping and have on several occasions found it necessary to combat the fall in blood pressure with infusions while the patient was on the operating table.

The following results in regard to the motor activity of the intestine were obtained after intestinal stripping and after simple relief of intestinal obstruction:

In the group of animals in which obstruction had existed for forty-eight hours the intravenous injection of concentrated lactate-Ringer solution twenty-four hours after the relief of the obstruction invariably resulted in an increase in intestinal activity, both in the group in which simple relief of the obstruction had been effected and in the group in which stripping of the intestine had been performed. The average increases in intestinal tone and amplitude of the peristaltic movements and the average duration of increased intestinal activity were greater in the group

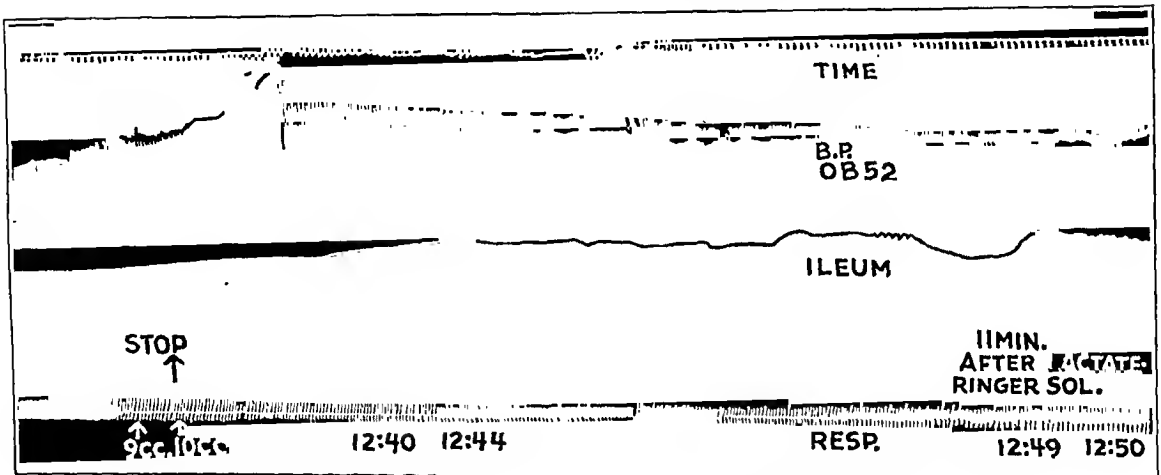


Fig. 3.—Kymographic tracing showing intestinal activity twenty-four hours after mechanical relief by stripping of an intestinal obstruction which had been existent forty-eight hours. As shown by the arrow at the left, 10 cc. of twenty times normal lactate-Ringer solution was given intravenously. Following this there was increase in tone in the intestine (ileum), which persisted throughout the experiment. The increased tone, however, was not marked at any time.

of animals in which simple relief of obstruction was produced than in the group in which intestinal stripping (fig. 2) was performed. In the group in which obstruction had been present for forty-eight hours, twenty-four hours after simple relief of the obstruction and immediately after intravenous administration of the hypertonic salt solution, there was increase in the activity of the intestine in all (100 per cent) of the animals (two observations). The average increase in intestinal tone was 9.5 mm., the average increase in amplitude 0.75 mm. and the average duration of increased activity thirty minutes. In the group of animals in which stripping was performed (two observations) there was increase in the activity of the intestine in 100 per cent of the instances; the average increase in tone was 8.5 mm., the average increase in amplitude 0.5 mm. and the average duration twenty-six and a half minutes.

The results in these groups of experiments demonstrate that there is intestinal motility twenty-four hours after the relief of obstruction which had been present forty-eight hours, both in the animals in which simple relief of the obstruction was effected and in the animals in which the intestine was also stripped. After the intravenous injection of hypertonic salt solution the intestinal activity was increased in every instance in both groups. There was, however, a difference in the two groups as regards the character of the response; i. e., in the first group the increase in intestinal activity was greater and the action more prolonged than in the second group. Examples of the kymographic tracings

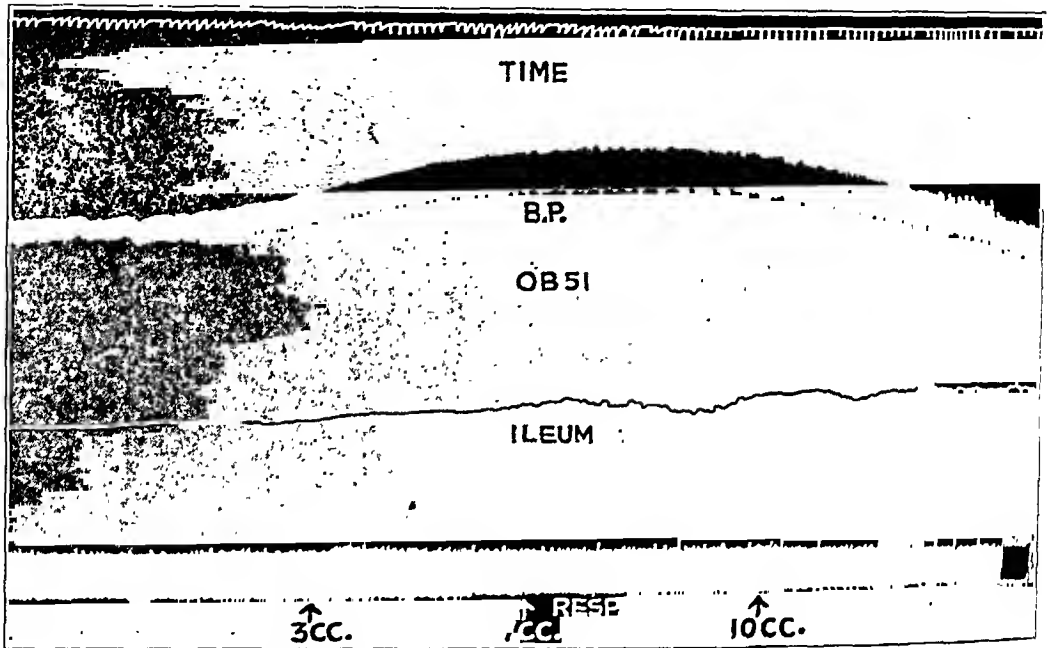


Fig. 4.—Kymographic tracing showing intestinal activity twenty-four hours after simple relief of an intestinal obstruction of forty-eight hours' duration. As shown by the arrows, as little as 3 cc. of twenty times normal lactate-Ringer solution produced increase in the tone of the intestine (ileum), which became more marked as the quantity injected was increased to 10 cc.

obtained for the animals in which obstruction had been present for forty-eight hours are shown in figures 3 and 4.

Eighteen observations were made on animals in which obstruction had existed for seventy-two hours, seven of which were made on animals in which simple relief had been produced and eleven on animals in which stripping and relief of the obstruction (fig. 5) had been carried out. In the first group there were increase in intestinal activity in 85.7 per cent of the instances and no change in activity in 14 per cent; the average increases in tone and amplitude of movement were 11.8 and 0.83 mm., respectively, and the average duration of the increased intestinal

activity was twenty and six-tenths minutes. In the second group of animals, in which the intestine had been stripped, the intestinal activity was increased in 81 per cent of the instances, was not changed in 9 per cent and was decreased in 9 per cent. The average increases in tone and amplitude of movement were 16.7 and 1 mm., respectively. The average duration of increased activity was eighteen and eight-tenths minutes.

The results obtained for the animals in the two groups in which obstruction had existed for seventy-two hours show a higher percentage of instances in which intestinal activity was increased and a longer duration of the increased activity in the animals in which simple relief of the obstruction was secured. The increases in tone and amplitude of movement in the animals in this group were slightly less than those in the animals in which stripping of the intestine had been performed. Figures 6 and 7 show kymographic tracings made from animals in the group in which obstruction had been present for seventy-two hours.

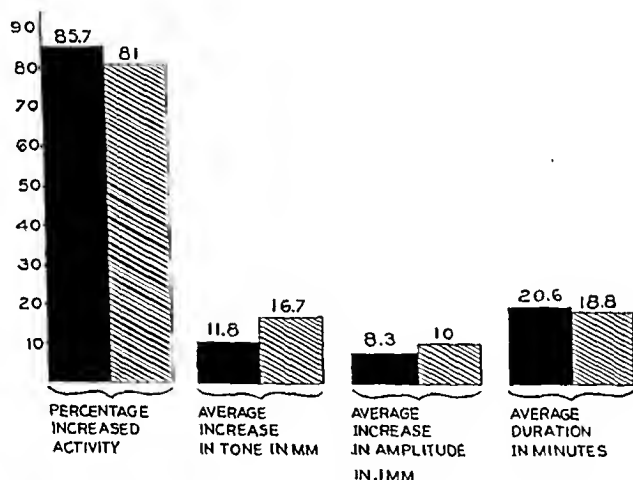


Fig. 5.—Graphic representation of intestinal activity twenty-four hours after relief of an obstruction of seventy-two hours' duration, following the intravenous administration of 10 cc. of twenty times normal lactate-Ringer solution. For the group in which simple relief was produced, seven observations were made, and for the group in which stripping was performed, eleven observations were made.

Thirty-four observations were made on animals in which intestinal obstruction had been present for ninety-six hours, thirteen of which were on animals in which simple relief of the obstruction was produced and twenty-one on animals in which relief of the obstruction and stripping of the intestine were carried out (fig. 8). In the first group of observations the intestinal activity was increased in 76.9 per cent of the instances and was not changed in 23 per cent. The average increases in tone and amplitude of intestinal movement were 17.9 and 0.8 mm., respectively. The average duration of the intestinal activity was seventeen and four-tenths minutes. In the second group of observations, on animals in which the intestine was stripped, the intestinal activity was increased in 76.1 per cent of the instances, was not changed in 19.4 per cent and was decreased in 4.2 per cent. The average

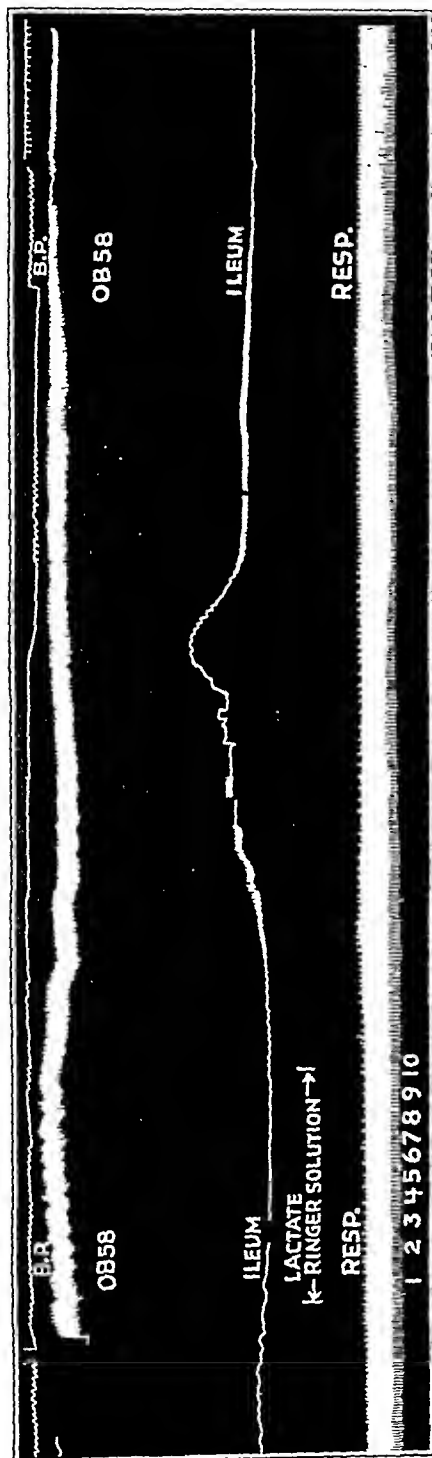


Fig. 6.—Kymographic tracing showing intestinal activity twenty-four hours after mechanical relief by stripping of an obstruction which had been present for seventy-two hours. Following the intravenous administration of twenty times normal lactate-Ringer solution, as illustrated in the portion of the tracing at the left, there was increase in intestinal tone and some increase in intestinal movement, which, however, lasted a relatively short period.

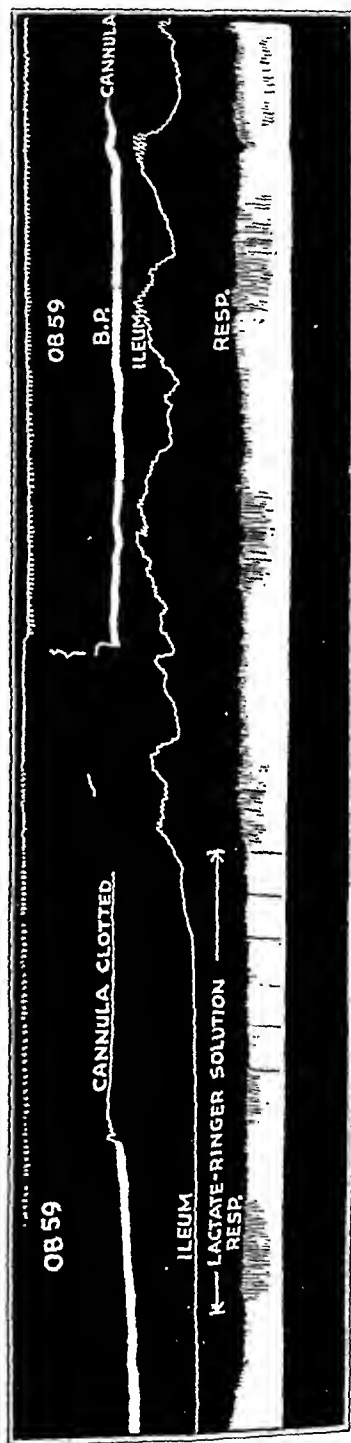


Fig. 7.—Kymographic tracing showing intestinal activity twenty-four hours after simple relief of intestinal obstruction of seventy-two hours' duration. As shown in the portion of the kymographic tracing on the left, following the intravenous administration of 10 cc. of twenty times normal lactate-Ringer solution there was definite increase in intestinal activity, consisting of increase in tone and movement. This persisted throughout the experiment.

increases in intestinal tone and amplitude of movement were 5.7 and 0.6 mm., respectively. The duration of the increased activity was thirteen and seven-tenths minutes.

The percentages of instances in which activity was increased were about the same in the two groups of animals. The particular difference between the two groups was the greater average increase (17.9 mm. as compared with 5.7 mm.) in intestinal tone in the group in which simple relief of the obstruction was produced than in the group in which stripping was performed. The duration of the increased activity was longer in the former group (seventeen and four-tenths minutes) than in the latter group (thirteen and seven-tenths minutes). Kymographic tracings made on two of the animals in the group in which obstruction was present for ninety-six hours are shown in figures 9 and 10.

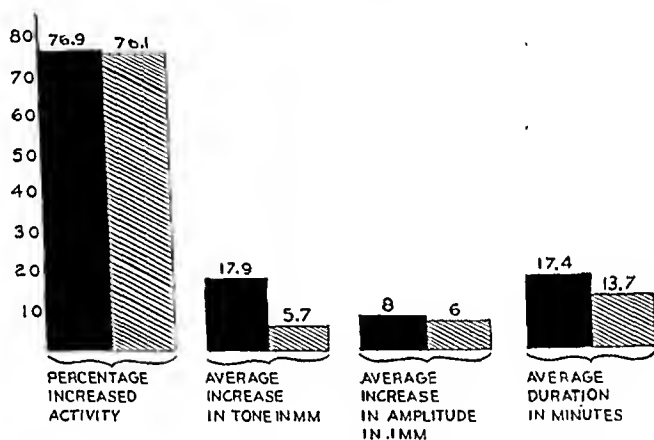


Fig. 8.—Graphic representation of intestinal activity twenty-four hours after obstruction of ninety-six hours' duration, following the intravenous administration of 10 cc. of twenty times normal lactate-Ringer solution. For the group in which simple relief was produced, thirteen observations were made, and for the group in which stripping was also performed, twenty-one observations were made.

Seventeen observations were made on animals in which obstruction had been present for one hundred and twenty hours, eight of which were on animals in which simple relief was produced and nine on animals in which relief of the obstruction and stripping of the intestine were effected (fig. 11). In the first group the intestinal activity was increased in 87.5 per cent of the instances and was not changed in 12.5 per cent. The average increases in intestinal tone and amplitude of intestinal movement were 24 and 3.3 mm., respectively. The average duration of the increased activity was twenty-two and one-tenth minutes. In the second group of animals, in which the intestine was stripped, the intestinal activity was increased in 88.8 per cent of the instances and was not changed in 11.1 per cent. The average increases in tone and amplitude of movement were 11.5 and 0.8 mm., respectively. The average duration of the increased intestinal activity was twenty-one and three-tenths minutes.



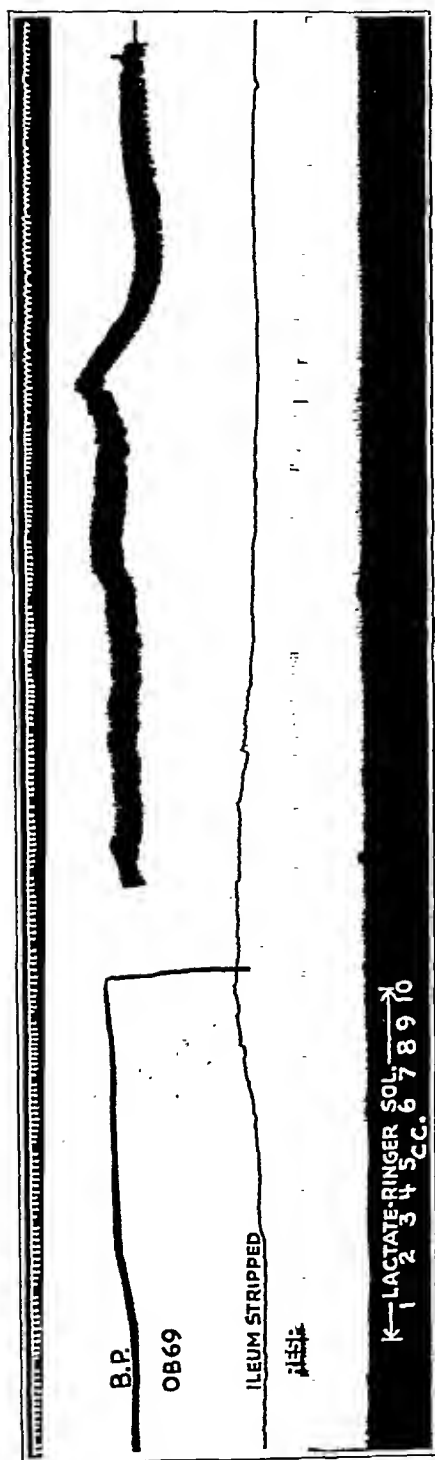


Fig. 9.—Kymographic tracing showing intestinal activity twenty-four hours after mechanical relief by stripping of an intestinal obstruction of ninety-six hours' duration. Following the intravenous administration of 10 cc. of twenty times normal lactate-Ringer solution as shown in the portion of the tracing on the left, there was slight increase in intestinal tone and movement.



Fig. 10.—Kymographic tracing showing intestinal activity twenty-four hours after simple relief of obstruction of ninety-six hours' duration. There was definite increase in tone, followed by increase in movement.

In the two groups in which obstruction had existed for one hundred and twenty hours the percentage of instances in which intestinal activity was increased were about the same. There was, however, considerable difference in the character of the response of the intestine; i. e., the average increases in tone and amplitude of movement in the group in which simple relief of the obstruction was effected were 24 and 3.3 mm., respectively, whereas in the group in which the intestine was stripped these values were 11.5 and 0.8 mm., respectively. Examples of kymographic tracings for this group are shown in figures 12 and 13.

Thirty-five observations were made on animals in which intestinal obstruction had been present for one hundred and forty-four hours, sixteen of which were on animals in which simple relief was produced and nineteen in animals in which relief of the obstruction and stripping of the intestine were carried out (fig. 14). In the first group the intestinal activity was increased in 87.5 per cent of the

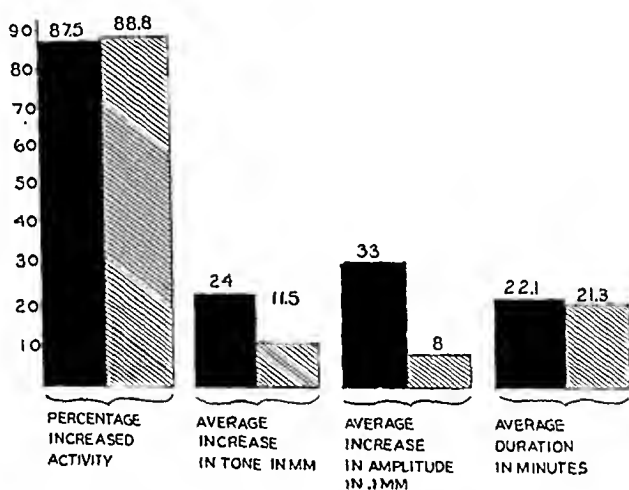


Fig. 11.—Graphic representation of intestinal activity twenty-four hours after obstruction of one hundred and twenty hours' duration, following the intravenous administration of 10 cc. of twenty times normal lactate-Ringer solution. For the group in which simple relief was produced, eight observations were made, and for the group in which stripping was also performed, nine observations were made.

instances and was not changed in 12.5 per cent. The average increases in intestinal tone and amplitude of movement were 9.2 and 2.8 mm. The average duration of the increased intestinal activity was nineteen and one-tenth minutes. In the second group the intestinal activity was increased in 94.7 per cent of the instances and was not changed in 5.3 per cent. The average increases in tone and amplitude of movement were 10 and 1.5 mm., respectively. The average duration of increased activity was twelve minutes.

In the groups in which obstruction had been present for one hundred and forty-four hours there was a slighter increase in intestinal activity in the group in which stripping was performed than in the group in



Fig. 12.—Kymographic tracing showing intestinal activity twenty-four hours after mechanical relief by stripping of an intestinal obstruction of one hundred and twenty hours' duration. Following the intravenous administration of 10 cc. of twenty times normal lactate-Ringer solution, as shown in the portion of the kymographic tracing on the left, there was slight increase in intestinal movement and practically none in intestinal tone.



Fig. 13.—Kymographic tracing showing intestinal activity twenty-four hours after simple relief of an intestinal obstruction of one hundred and twenty hours' duration. As shown in the portion of the kymographic tracing on the left, the intravenous administration of 10 cc. of twenty times normal lactate-Ringer solution produced definite increase in intestinal tone and slight increase in intestinal movement. Although the increase in tone was not marked throughout the experiment, the increase in activity persisted.

which simple relief of the obstruction was produced. The average increase in tone (10 mm.) in the first group was slightly higher than that (9.2 mm.) in the second group. In the group in which simple relief was produced the increase in amplitude of intestinal movement (2.8 mm.) was greater and the duration of increased activity (nineteen minutes) longer than the corresponding values for amplitude (1.5 mm.) and duration (twelve minutes) in the group in which stripping was performed. Figures 15 and 16 show two of the kymographic tracings obtained for animals in this group.

## COMMENT

A total of one hundred and eight observations were made concerning the intestinal activity twenty-four hours after the relief of intestinal

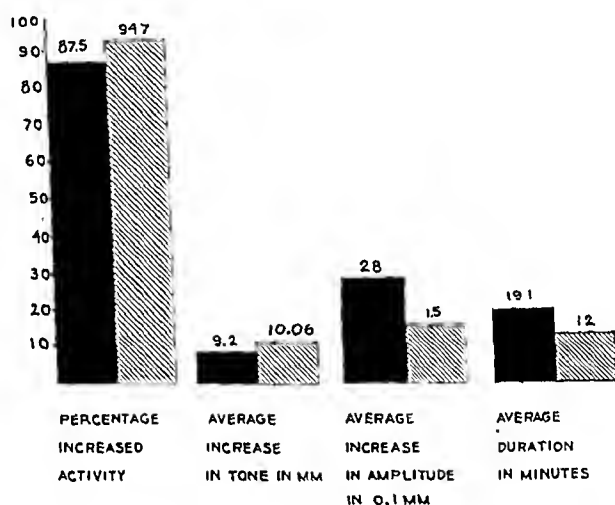


Fig. 14.—Graphic representation of intestinal activity twenty-four hours after obstruction of one hundred and forty-four hours' duration, following the intravenous administration of 10 cc. of twenty times normal lactate-Ringer solution. For the group in which simple relief of obstruction was produced, sixteen observations were made, and for the group in which stripping was also performed, nineteen observations were made.

obstruction existing for periods varying from forty-eight to one hundred and forty-four hours. In each instance the activity of the intestine was determined by its response to the intravenous injection of 10 cc. of twenty times normal lactate-Ringer solution. Forty-six observations were made on animals in which simple relief of the obstruction had been produced and sixty-two observations on animals in which, in addition to the relief of the obstruction, the intestine was emptied of its contents by stripping. In the former group there was increase in intestinal activity in 84.7 per cent of the instances and no change in 15.2 per cent, and in the latter group there was increase in intestinal



Fig. 15.—Kymographic tracing showing intestinal activity twenty-four hours after the mechanical relief by stripping of an intestinal obstruction of one hundred and forty-four hours' duration. Following the intravenous administration of 10 cc. of twenty times normal lactate-Ringer solution there was definite increase in intestinal tone and amplitude of movement, as shown in the portion of the kymographic tracing on the left.

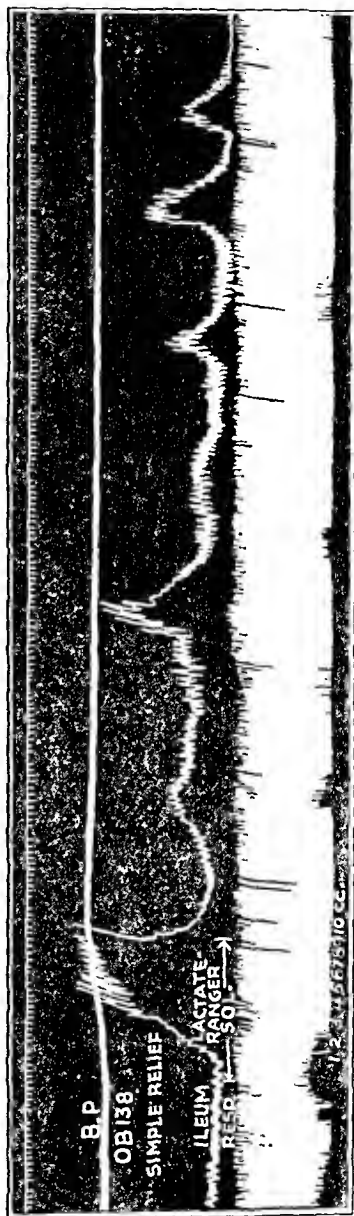


Fig. 16.—Kymographic tracing showing intestinal activity twenty-four hours after simple relief of an intestinal obstruction of one hundred and forty-four hours' duration. An unusually pronounced increase in tone and amplitude of intestinal movement began after the intravenous administration of the first 2 cc. of twenty times normal lactate-Ringer solution.

activity in 83.8 per cent, no change in 11.2 per cent and a decrease in 4.8 per cent (fig. 17). The decrease in activity was observed in two animals, in one of which obstruction had been present for seventy-two hours and in the other, for ninety-six hours, and in both instances decrease in intestinal tone occurred. The average increases in tone and amplitude of intestinal movement for the groups in which simple relief of the obstruction was accomplished were 15.5 and 1.69 mm., respectively, whereas for the groups in which stripping was also used the corresponding values were 10.1 and 1.06 mm. (fig. 18). The average duration of the increased activity in the groups in which simple relief of the obstruction was produced was twenty-one and eight-tenths minutes, whereas in the groups in which stripping was used the duration was fifteen and eight-tenths minutes (fig. 18). As already stated, stripping of the intestine in mechanical obstruction in order to empty the bowel of its accumulated

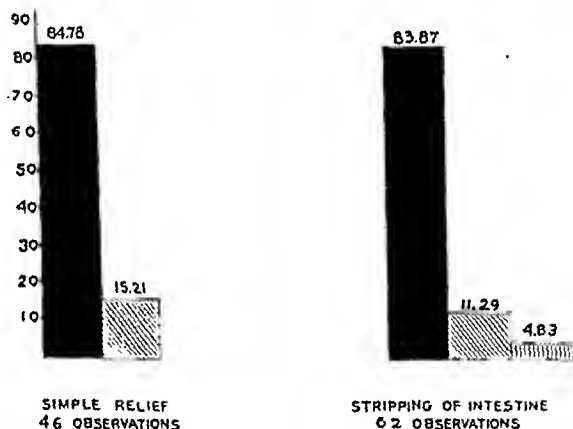


Fig. 17.—Graphic representation of the relative effects on intestinal activity of simple relief and of relief by mechanical stripping of the intestine in the treatment of ileus of all periods of duration. The increase in activity was practically the same in the two groups of animals, the only perceptible difference being that in one instance in which stripping had been performed there was an actual decrease in the intestinal activity. In this graph the values for the group in which there was increase in activity are expressed by black areas; those for the group in which there was no change in activity, by areas of cross-hatching, and those for the group in which there was decrease in activity, by areas of vertical lines.

gas and fecal material is theoretically a desirable procedure because by decreasing the intra-intestinal tension the pressure on the intramural blood vessels is relieved and the blood supply to the intestine improved. By improving the blood supply to the bowel and decreasing the intra-intestinal pressure the muscular activity should be improved, unless the trauma to the intestinal wall, with its resultant deleterious effects, inhibits muscular contraction. The results obtained in the present investigation

indicate that intestinal activity following obstruction is not improved by stripping of the intestine but that, on the contrary, the activity following simple relief of the obstruction is greater (figs. 17 and 18). If the advantages of stripping are not greater than those of simple relief of intestinal obstruction it is obvious that the former procedure has no place in the treatment of ileus, for its dangers are considerable. The immediate lowering of blood pressure, even in normal persons but especially in patients whose cardiovascular system is already taxed, is a serious objection to the method and in many cases precludes its use. In addition to this, the increased danger of spillage of intestinal contents and contamination of the peritoneum during the stripping process in itself almost contraindicates the procedure. Frequently in cases in which the intestinal distention is extreme the gentlest manipulation

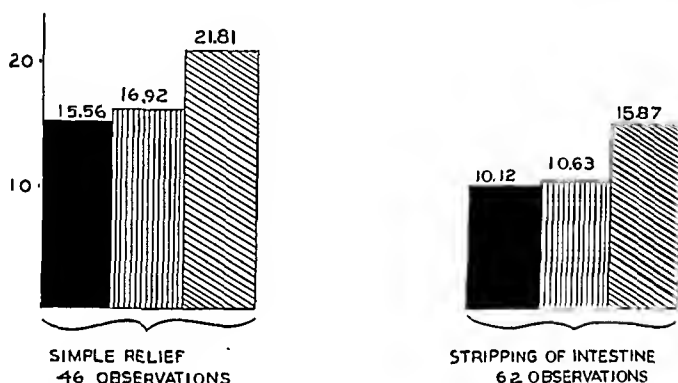


Fig. 18.—Graphic comparison of the character of the intestinal activity in the treatment of ileus of all periods of duration with simple relief and with relief and stripping. It is seen that the activity twenty-four hours after simple relief was definitely greater than after a similar period after stripping, the increase in tone (indicated by black areas) for the two groups being 15.5 and 10.1 per cent, respectively. The increase in amplitude (indicated by areas of vertical lines) was 1.69 and 1.06 mm., respectively, and the average duration of the increase in activity (indicated by areas of cross-hatching), 21.8 and 15.8 minutes, respectively.

results in rupture of the intestine because of the marked vascular changes. Stripping of the intestine in such instances would produce irreparable damage.

#### CONCLUSIONS

The production of relief of intestinal distention in mechanical obstruction by stripping of the intestine theoretically should improve intestinal muscular activity by improving the vascularity.

In order to evaluate the results obtained by simple relief of intestinal obstruction as compared with the results obtained by stripping of the intestine, the present investigation was undertaken. The intestinal activ-

ity was determined twenty-four hours after the relief of obstruction which had been existent for periods varying from forty-eight hours to one hundred and forty-four hours.

The results obtained demonstrate that the relief of intra-intestinal tension by stripping does not increase the activity of the intestine, probably because of the trauma to the bowel produced by the stripping process.

As intestinal stripping offers no advantage over simple relief of obstruction, the procedure is not justified clinically because of the detrimental effects on the cardiovascular system and the greater danger of spillage of intestinal contents and peritoneal contamination.



# ENDOCHOLEDOCHAL SECTION OF THE SPHINCTER OF ODDI

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The relationship of the sphincter of Oddi to the physiologic and pathologic processes of the biliary tract has received increasing attention during the past decade. Attempts have been made to associate certain aspects of cholecystitis and cholelithiasis, acute pancreatitis and various forms of jaundice with a dysfunction of this muscle. Some of the symptomatology referable to the upper part of the abdomen in cases in which the diagnosis is obscure and many of the poor results following cholecystectomy have been attributed to dyskinesia of the sphincter. It has been suggested that it may be desirable to produce a concomitant incompetence of the sphincter of Oddi in many instances in which function of the gallbladder has been partially destroyed by disease or completely lost by operative removal. An experimental investigation of this problem forms the basis of the present communication.

The anatomist Gage<sup>1</sup> first described the sphincter of the common bile duct in the cat as early as 1879. Several years later, in order to explain the finding of a dilated biliary tract in cases in which the function of the gallbladder had been lost, Oddi<sup>2</sup> accurately described the sphincter of the common bile duct both in man and in animals. His observations were confirmed subsequently by the researches of Hendrickson<sup>3</sup> and Helly<sup>4</sup> and recently by those of Mann,<sup>5</sup> Porsio<sup>6</sup> and Nagai and Sativada.<sup>7</sup>

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1. Gage, S. H.: The Ampulla of Vater and the Pancreatic Ducts in the Domestic Cat (*Felis Domestica*), *Am. Quart. Micr. J.* **1**:128, 1879.

2. Oddi, R.: D'une disposition à sphincter spéciale de l'ouverture du canal cholédoque, *Arch. de biol.* **8**:317, 1887.

3. Hendrickson, W. F.: A Study of the Musculature of the Entire Extra-Hepatic Biliary System, Including That of the Duodenal Portion of the Common Bile Duct and of the Sphincter, *Bull. Johns Hopkins Hosp.* **9**:221, 1898.

4. Helly, K. K.: Die Schliessmuskulatur an den Mündungen der Gallen- und der Pankreasgänge, *Arch. f. mikr. Anat.* **54**:614, 1899.

5. Mann, F. C., and Giordano, A. S.: The Bile Factor in Pancreatitis, *Arch. Surg.* **6**:1 (Jan.) 1923.

(Footnotes continued on next page)

The resistance to the passage of fluid from the common bile duct into the duodenum is apparently due to several factors, the most important of which is the tonus of the sphincter of Oddi. To this, however, must be added the diagonal passage of the duct within the duodenal wall and the tonus of the duodenal smooth muscle and of its muscularis mucosae. For the sake of brevity, we shall refer to these composite resisting factors as the sphincteric mechanism. This resistance of the sphincteric mechanism in dogs lies between 100 and 200 mm. of water<sup>8</sup> and is markedly increased by irritation, such as that produced by the application of dilute hydrochloric acid to the papilla of Vater.<sup>9</sup> Irritation of the gastric mucosa, distention of the stomach, starvation and the ingestion of drugs which act on the autonomic nervous system<sup>10</sup> all produce alterations in the resistance of the sphincteric mechanism.

This resistance can be overcome by the contractile force of the gall-bladder, which is equivalent to about from 200 to 300 mm. of water.<sup>11</sup>

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6. Porsio, A.: Structure of the Intraparietal Portion of the Human Bile Duct and Pancreatic Duct, with Special Reference to Oddi's Sphincter, *Arch. ital. di anat. e di embriol.* **29**:127, 1931.

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8. Giordano, A. S., and Mann, F. C.: The Sphincter of the Choledochus, *Arch. Path.* **4**:943 (Dec.) 1927.

9. (a) Oddi, R.: Sulla tonicità dello Sfintere del Coledoco, *Arch. per le sc. med.* **12**:333, 1888. (b) Archibald, E.: Experimental Production of Pancreatitis in Animals as a Result of Resistance of Common Duct Sphincter, *Surg., Gynec. & Obst.* **28**:529, 1919.

10. Cole, W. H.: Relation of Gastric Content to Physiology of Common Duct Sphincter, *Am. J. Physiol.* **72**:39, 1925. Burget, G. E.: The Regulation of the Flow of Bile: II. Effect of Eliminating the Sphincter of Oddi, *ibid.* **79**:130, 1926. Brugsch, T., and Horsters, H.: Chologoga und Chologogie, *Arch. f. exper. Path. u. Pharmacol.* **118**:267, 292 and 305, 1926. Nakashima, K.: Studies on Mode of Bile Outflow, About Oddi's Sphincter, Regulator of Bile Outflow, *Acta scholae, med. univ. imp., Kioto* **9**:357, 1927. Kitakoji, Y.: Studien über die Funktionen der Gallenblase und des Oddischen Muskels in Bezug auf die Absonderung der Blassengalle: Ueber den Einfluss von Nervengiften auf die Funktionen der Gallenblase und des Oddischen Muskels, *Nagoya J. M. Sc.* **5**:24, 1930. Shi, K.: Influence of Gall Bladder, Oddi's Muscle and Duodenum on Outflow of Bile: Injection of Visceral Nerve Poisons and Pituitrin, *Jap. J. Gastroenterol.* **5**:19, 1933.

11. McMaster, P. D., and Ehnman, R.: The Physiological Variations in Resistance to Bile Flow to the Intestine, *J. Exper. Med.* **44**:155, 1926; On the Expulsion of Bile by the Gall Bladder, and a Reciprocal Relationship with the Sphincter Activity, *ibid.* **44**:173, 1926. Higgins, G. M., and Mann, F. C.: Physiological and Anatomical Considerations of the Sphincteric Mechanism of the Choledochus, *Anat. Rec.* **35**:13, 1927.

Ordinarily, however, as many investigators<sup>12</sup> have shown, the sphincter tends to relax as the gallbladder contracts; this is known as the law of contrary innervation. Hamrick<sup>13</sup> and others have emphasized that this reciprocal action does not always occur, since a number of substances which relax the sphincter do not cause a contraction of the gallbladder.

In addition, many other factors which disturb the nervous mechanism of the gastro-intestinal tract often interfere with this reciprocal action. It has been suggested that some of these factors may have a constitutional basis<sup>14</sup> or be related to the menstrual cycle and pregnancy<sup>15</sup> or be due to psychic disturbances.<sup>16</sup> Nanu-Muscel and Pavel<sup>17</sup> have presented cases in which exploratory laparotomy proved that a pre-existing jaundice must have been due to spasm of the sphincter caused by psychic trauma, as icterus recurred after a fright.

It is well known that the sphincter of Oddi rapidly loses its tone after cholecystectomy, and its resistance falls from 150 to 40 or 50 mm. of water.<sup>18</sup> The flow of bile then becomes continuous, although if the ducts dilate it may become intermittent.<sup>19</sup> The activity of the sphincter meanwhile is merely dormant, for either local irritation or nervous stimulation will often cause the sphincter to regain its former tonus or to become spastic. This may be one of the factors leading to the dilatation of the extrahepatic biliary tract after cholecystectomy, which has been noticed since the time of Oddi.

Rost,<sup>19</sup> Westphal,<sup>15</sup> Liek<sup>20</sup> and others have felt that many of the untoward symptoms following cholecystectomy were often due to spasm of the sphincter of Oddi. Various therapeutic measures have been sug-

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13. Hamrick, R. A.: The Emptying of the Gall Bladder: Experimental Study, *Am. J. M. Sc.* **174**:168 (Aug.) 1927.

14. Kaufmann, J.: Role of Spasticity in Diseases of Digestive Tract: Case of Visceral Tetany, Causing Acute Cholangitis and Pancreatitis, *Am. J. M. Sc.* **166**: 67 (July) 1923.

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16. Ivy, A. C.; Voegtlin, W. L., and Greengard, H.: The Physiology of Common Duct: A Singular Observation, *J. A. M. A.* **100**:1319 (April 29) 1930.

17. Nanu-Muscel, I., and Pavel, I.: Le spasme du sphincter d'Oddi cause de certains ictères prolongés, *Presse méd.* **38**:1260, 1930.

18. Judd, E. S., and Mann, F. C.: The Effect of Removal of the Gall Bladder, *Surg., Gynec. & Obst.* **24**:437 (April) 1917.

19. Rost, F.: Die funktionelle Bedeutung der Gallenblase: Experimentelle und anatomische Untersuchungen nach Cholecystektomie, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **26**:710, 1913.

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gested to relieve this. Blass<sup>21</sup> and others obtained good results by the administration of magnesium sulfate by a duodenal tube. Archibald<sup>22</sup> attempted to keep the sphincter of Oddi relaxed by frequent feedings. Some surgeons<sup>23</sup> have forcibly stretched the muscle with dilators through the common duct in order to abolish its function for several months. Del Valle and Donovan<sup>24</sup> proposed section of the sphincter of Oddi for functional disorders.

Archibald<sup>22</sup> found that cutting the sphincter transduodenally in cats lowered its resistance from 600 to 70 mm. of water.<sup>9b</sup> These experiments were repeated by Judd and Mann,<sup>18</sup> who found the residual resistance after section of the sphincter to vary from 0 to 120 mm. of water in dogs and cats.

Coffey<sup>25</sup> has shown in his experimental work on the common bile duct and on the transplantation of the ureter into the colon that the oblique course of a duct through the wall of a hollow viscus produces the effect of a one way valve. This prevents ascending infection through reflux of the intestinal contents. Therefore, if it is desirable to section the sphincter of Oddi, some method should be evolved that would accomplish this without completely dividing the intramural portion of the choledochus. In addition, the operative procedure would be greatly simplified and rendered less dangerous if section of the sphincter were carried out without opening the duodenum.

#### EXPERIMENTAL WORK

A series of experiments were devised to test the practicality of endocholedochal division of the sphincter of Oddi, avoiding, however, complete section of the intramural portion of the common bile duct. Such a procedure would obviate the necessity of opening the duodenum and, by leaving a part of the intramural portion of the common bile duct intact, prevent the reflux of duodenal contents with the danger of ascending infection. Accordingly, an instrument was constructed to divide the sphincter of Oddi safely through the choledochus. The final design of the sphincterotomy<sup>26</sup> was evolved only after a number of technical

21. Blass, G.: Treatment of Recurrent Pain Caused by Congestion of Bile Ducts from Spastic Contraction After Cholecystectomy, *Wien. klin. Wchnschr.* **41**:1429 (Oct. 11) 1928.

22. Archibald, E.: Personal communication to the authors.

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25. Coffey, R. C.: Transplantation of Ureters into Large Intestine in Absence of Functioning Urinary Bladder, *Surg., Gynec. & Obst.* **32**:383, 1921.

26. Manufactured by the American Cystoscope Makers, Inc., New York.

failures, for the curve of the instrument and the length and the shearing strength of the cutting blade had to be constantly altered so that it could easily pass down the cystic and common bile ducts and safely divide the sphincter of the dog. The sphincterotome (fig. 1) consists of a curved hollow shaft 20 cm. long from the handle to the tip and 2.5 mm. in diameter. The tip, however, is flattened from side to side so as to be 4 mm. in width for a length of 3 cm. This flattened tip is slotted to receive a closely fitting blade 16 mm. long, 2 mm. broad and 1 mm. thick. The blade rotates on a pin of specially hardened steel and is moved by a wire which runs through the shaft and is connected to the outer movable handle of the instrument. Closure of the handles results in the movement of the opened blade, which acts in reverse fashion through the slot. The resulting shearing force punches out a piece of tissue 1 mm. in thickness and about 8 mm. in length.

The sphincterotome is introduced through the cystic duct into the choledochus and passed down until the tip of the instrument enters the duodenum via the papilla of Vater (fig. 2 *A*). The blade, which acts in reverse fashion as described, is opened (fig. 2 *B*). The instrument is then withdrawn, and the cutting edge automatically impinges on the anterior lip of the papilla (fig. 2 *C*). The duodenum

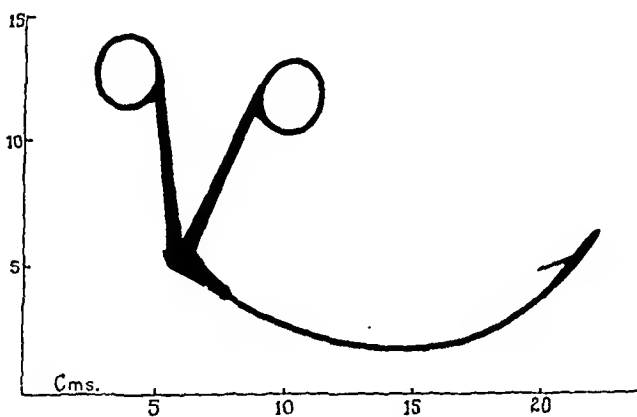


Fig. 1.—The sphincterotome.

is pulled downward, and as the instrument is pulled upward firmly the sphincterotome is closed, cleanly dividing the sphincter of Oddi (fig. 2 *D*). After the instrument has been withdrawn, the cystic duct is tied, and the gallbladder is removed.

All experiments were performed on dogs under anesthesia with sodium secondary butyl-beta-bromallyl barbituric acid. Operations were such that biliary drainage was not necessary. There were no subsequent signs of leakage of bile, peritonitis or pancreatitis. The resistance of the sphincter was measured in many animals by inserting into the common bile duct a cannula with a manometer attached. The duodenum was then opened, and the manometric height at which the fluid began to flow through the papilla was noted. As a further indication of functional activity of the sphincter half-normal hydrochloric acid was applied to the papilla and the resistance read again.

The experiments were performed in various groups as follows:

1. The estimation of the resistance of the sphincter of Oddi in normal dogs.
2. The estimation of the resistance of the sphincter of Oddi after cholecystectomy.
3. The effect of sphincterotomy with the gallbladder left intact.

4. The effect of simultaneous cholecystectomy and sphincterotomy.
5. The effect of sphincterotomy after cholecystectomy.

GROUP 1.—The resistance of the sphincter of Oddi was measured in six normal dogs under anesthesia with sodium secondary butyl-beta-bromallyl barbituric acid, both before and after the application of hydrochloric acid to the papilla of Vater. The results are summarized in table 1. The average figures were 153 mm. of water before and 296 mm. after the application of hydrochloric acid. The resistance of the normal sphincter was doubled when hydrochloric acid was applied to the papilla.

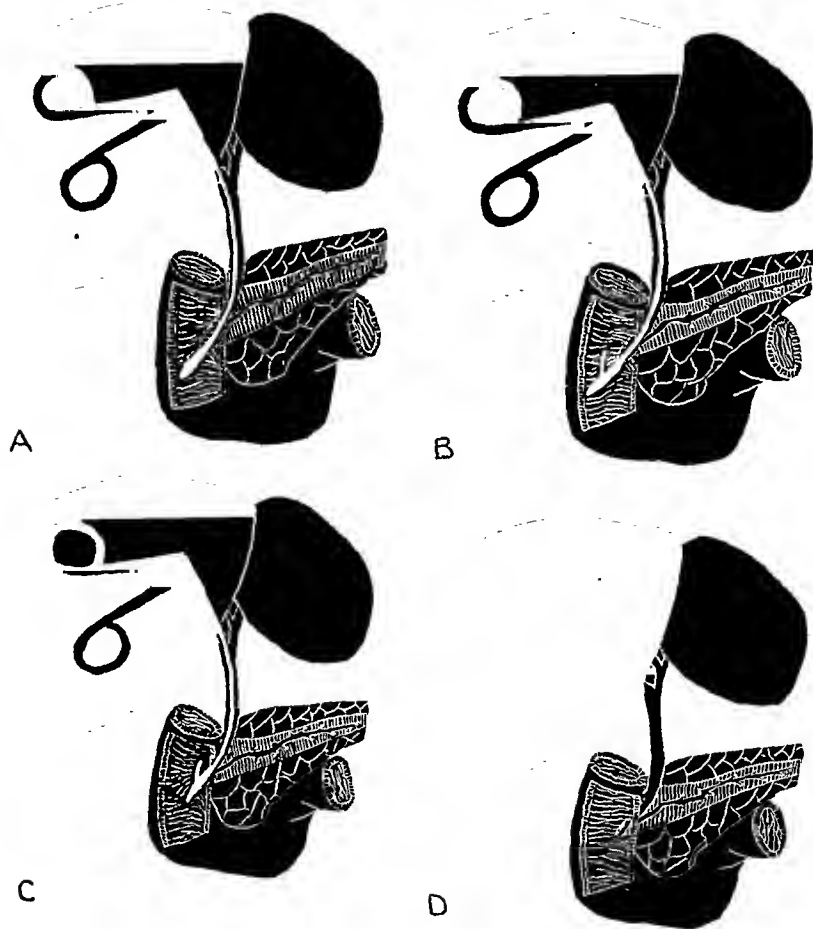


Fig. 2.—Technic of endocholedocal section of the sphincter of Oddi. In *A*, the sphincterotome is passed down the cystic and the common bile duct, through the papilla and into the duodenum. In *B* when the flattened end of the sphincterotome has entered the duodenum, the knife blade is opened. In *C*, the sphincterotome is pulled back until the knife blade impinges on the anterior lip of the papilla. In *D*, the knife blade is closed, sectioning the sphincter of Oddi. After withdrawing the sphincterotome the cystic duct is tied.

GROUP 2.—The effect of simple cholecystectomy on the tonus of the sphincter of Oddi was investigated in five animals. The resistance was measured before

and after the application of hydrochloric acid to the papilla at varying periods after cholecystectomy. The results are summarized in table 2. The resistance was measured two days after cholecystectomy in two animals. In one it was high, while in the other it had fallen below normal. Two other animals, in which the resistance was measured four and six months, respectively, after cholecystectomy, showed a loss of sphincteric tone. One animal (56), which was operated on four months after cholecystectomy, was found to be pregnant; the rather high initial resistance of the sphincter may have been due to this condition.<sup>15</sup> However, irritation of the sphincter by the topical application of acid produced spasm in all the animals.

Histologic sections of the common and intrahepatic bile ducts and liver were studied in these animals. Scattered collections of lymphocytes and occasional

TABLE 1.—*Resistance of the Sphincter of Oddi in Normal Dogs*

Animal No.	Resistance of Sphincter of Oddi Before Adding HCl, Mm. of H <sub>2</sub> O	Resistance of Sphincter of Oddi After Adding HCl, Mm. of H <sub>2</sub> O
A.....	149	332
2A.....	130	224
3A.....	198	382
4.....	168	311
5.....	113	223
6.....	159	308
Average.....	153	296

TABLE 2.—*Resistance of the Sphincter of Oddi After Cholecystectomy*

Animal No.	Days After Chole- cystectomy Before Animal Was Killed	Diameter of Duct at Cholecystec- tomy, Mm.	Diameter of Duct After Cholecystec- tomy, Mm.	Resistance of Sphincter, Mm. of H <sub>2</sub> O	
				Before Application of HCl	After Application of HCl
73	2	4	5	225	310
77	2	3	4	109	250
38	120	6	6	83	242
56	120	3	3	120	240
45	180	4	5	55	233

plasma cells were seen in the subepithelial connective tissue of the choledochus in two of the animals. Focal infiltration of the periportal connective tissue by polymorphonuclear leukocytes and lymphocytes was noted in one instance.

For comparative purposes, the bile ducts and liver of six normal dogs were examined. A slight to moderate lymphocytic infiltration of the subepithelial connective tissue of the choledochus and hepatic ducts was seen in all instances. The livers of four of the six animals showed lymphocytic and polymorphonuclear leukocytic infiltration of the periportal connective tissue. The extent of the infiltration varied from that of a few cells in one or more portal fields to foci of dense collections of polymorphonuclears and lymphocytes.

It is evident that the cellular infiltration observed in the experimental animals was no more extensive than that seen in the control group.

GROUP 3.—Three dogs were used to determine the effect of endocholedochal sphincterotomy with the gallbladder left intact. The contents of the gallbladder were aspirated with a large needle. The sphincterotome was inserted through the

same opening, and routine sphincterotomy was performed. The instrument was then withdrawn, the needle was reintroduced into the opening in the gallbladder and the bile which had been previously aspirated was reinjected, leaving the gallbladder and bile ducts distended with bile. The opening in the gallbladder was closed with purse-string suture. The results are summarized in table 3.

One animal was killed eight days after operation because of the onset of distemper. The gallbladder was found to be severely inflamed and contained rather thin light brown bile. The common bile duct was slightly dilated (6 mm. in diameter). Culture of material from the gallbladder showed the presence of *Bacillus Welchii*. Histologic examination showed acute and chronic inflammation of the gallbladder. The wall of the common bile duct was diffusely infiltrated by polymorphonuclear leukocytes. Foci of polymorphonuclear leukocytic infiltration of the periportal connective tissues were present in the liver. The latter, however, were not in excess of those seen in the normal control animals.

TABLE 3.—*Effect of Sphincterotomy with the Gallbladder Left Intact*

Animal No.	Days After Sphincterotomy Before Animal Was Killed	Diameter of Duct Before Sphincterotomy	Diameter of Duct After Sphincterotomy	Resistance of Sphincter, Mm. of H <sub>2</sub> O		Bacteriology of Gallbladder Bile	Pathologic Changes
				Before Application of HCl	After Application of HCl		
78	8	4	5	Not done	Not done	<i>B. Welchii</i>	Acute inflammation of gallbladder; common duct unaltered; slight to moderate polymorphonuclear leukocytic and lymphocytic periportal infiltration
81	30	4	4	112	114	<i>B. Welchii</i>	Acute and chronic inflammation of gallbladder with thickened wall; marked subacute inflammation of common duct; foci of periportal cellular infiltration
90	150	5	6	92	130	<i>B. coli</i> ; <i>B. proteus</i> ; <i>B. subtilis</i> ; <i>Enterococcus</i>	Acute and chronic inflammation of gallbladder; subacute inflammation of common duct; scattered foci of marked polymorphonuclear leukocytic and lymphocytic periportal infiltration

The second animal was killed one month after operation. The wall of the gallbladder was thickened and contained murky bile, which on culture showed a heavy growth of *B. Welchii*. The common bile duct was neither dilated nor thickened. The resistance of the sphincter was found to measure 120 mm. of water. The application of hydrochloric acid to the papilla produced no change in resistance. Histologic examination showed an acute and chronic inflammation of the gallbladder. The wall of the common bile duct was diffusely infiltrated by polymorphonuclear leukocytes. Foci of polymorphonuclear leukocytic infiltration of the periportal connective tissues were present in the liver but not in excess of the findings in many normal animals.

The third animal was killed five months after operation. The gallbladder was markedly thickened and contained light brown bile full of precipitated particles of pigment. Culture of the bile showed the presence of typical intestinal flora: *Bacillus coli*, *Bacillus proteus*, *Bacillus subtilis* and *Enterococcus*. The resistance



of the sphincter of Oddi was found to be 92 mm. of water, and the addition of hydrochloric acid raised it to 130 mm. Histologic examination of the gallbladder, common bile duct and liver presented the same picture as that noted in the second animal.

GROUP 4.—Cholecystectomy and sphincterotomy were simultaneously performed in twelve dogs. Five of the animals died within ten days after operation, while the remaining seven dogs were killed at periods varying from two to six months. The results are tabulated in table 4. There was no gross infection in the biliary tract at autopsy. The duodenal surface of the sectioned papilla was well healed.

TABLE 4.—*Effect of Simultaneous Cholecystectomy and Sphincterotomy*

Animal No.	Dilatation of Duet	Days After Operation Before Animal Was Killed
16.....	0	120 (Died of foot infection)
21.....	0	180
5.....	0	50
8.....	+	56
9.....	0	180
14.....	0	180
15.....	+	180
4.....	0	10 (Died of distemper)
6.....	0	10 (Died of distemper)
7.....	0	11 (Died of distemper)
13.....	0	8 (Died of distemper)
20.....	0	5 (Died of distemper)

TABLE 5.—*Effect of Sphincterotomy After Cholecystectomy*

Animal No.	Months After Chole- cystectomy Before Sphincter- otomy Was Performed	Months After Sphincter- otomy Before Animal Was Killed	Diameter of Duet After Chole- cystectomy, Mm.	Diameter of Duet After Sphincter- otomy, Mm.	Resistance of Sphincter, Mm. of H <sub>2</sub> O	
					Before Application of HCl	After Application of HCl
31	2	3	4	4	45	94
34	2	3	9	4	83	101
30	2	6	4	3	79	113
32	2	6	4	3	140	161
2	6	6	9	4	92	104
35	6	6	15	6	120	139
24	6	6	4	4	..	..
29	6	6	4	4	70	72
40	6	6	8	4	92	105
37	6	6	8	4	..	..

The mucosa covering the inferior edge was always hypertrophied into a polypoid mass which overlay the opening of the common bile duct. Dilatation of the biliary tract was present in only two animals. Microscopic examination of the bile ducts and liver did not reveal any significant pathologic changes.

It was possible to observe the early stage of healing in the sectioned sphincters of the five animals which died of distemper within ten days after operation. The incised edges of the papilla were found to be healed by the tenth day, and there was neither ascending infection nor obstruction, owing, possibly, to an edematous reaction at the point of section. Microscopically, sections of the ducts proximal to the papilla showed moderate hyperplasia of the mucosa.

GROUP 5.—There were nine dogs in this group; in four of these sphincterotomy was performed two months after cholecystectomy, and in the other five, six months

after cholecystectomy. There was little difficulty encountered in this second operation. The stump of the cystic duct was found and incised, the sphincterotome was introduced and the sphincter of Oddi was divided. Two animals were killed three months and the others six months after this procedure. The results are summarized in table 5. The common bile duct was markedly dilated in three animals after cholecystectomy. In these dogs the choledochus was found to be of normal diameter in one instance three months and in the others six months after section of the sphincter. The resistance of the sphincter measured less than normal in all but two animals. Application of hydrochloric acid to the papilla caused only a slight increase in the resistance of the sphincter. This slight increase could be prevented by elevating the polypoid mass of mucosa which overlay the orifice of the common bile duct. The irritation of the hydrochloric acid caused the muscularis mucosae to contract, and this appeared to force this polypoid mass into the choledochal aperture. In two dogs (32 and 33) the initial resistance was fairly high, equaling the resistance of the normal sphincter. However, the addition of acid raised the resistance only slightly, indicating some functional destruction of the sphincter. Culture of bile aspirated from the common duct in four dogs (2, 24, 29 and 32) gave no growth on aerobic and anaerobic mediums.

On microscopic examination the changes in the bile ducts and liver were identical with those seen in normal control animals. One dog (37) died of distemper five days after the second operation. Autopsy revealed that the common duct, which had been enlarged to a diameter of 8 mm. after the previous cholecystectomy, had shrunk to a normal diameter within five days after sphincterotomy.

#### COMMENT

The reports of a large number of investigators indicate that in dogs the average resistance of the sphincteric mechanism to the passage of fluid is about 150 mm. of water.<sup>8</sup> The resistance averaged 153 mm. in the series of six control animals and was doubled when the papilla was irritated by the local application of half-normal hydrochloric acid.

It has been stated that the sphincter becomes hypotonic after simple cholecystectomy in dogs.<sup>18</sup> The observations herein recorded tend to support this statement. However, the series is too small to warrant final conclusions. The resistance was found to be variable after cholecystectomy; in two dogs it was 225 and 109 mm. of water, respectively, two days after operation, and in three other animals, 83, 55 and 120 mm. from four to six months after operation. Irritation of the papilla uniformly increased this resistance, so that in five animals it averaged 225 mm. of water. Evidently the sphincter, which may become hypotonic after cholecystectomy, still retains the ability to become spastic on irritation.

The function of the sphincteric mechanism, as measured by its ability to go into spasm on irritation, was found to be markedly reduced after endocholedochal sphincterotomy. The resistance was 130 and 92 mm. of water, respectively, in two cases in which the gallbladder had been left intact. Application of acid to the papilla had no effect on the resistance of the first, while it raised the resistance of the second only

to 113 mm. of water. Measurements of the sphincteric resistance after simultaneous cholecystectomy and sphincterotomy were made in one case. It was measured on the fourth day after operation and was found to be 50 mm. before and 60 mm. after the application of acid to the papilla. This low resistance indicated not only that the sphincter had been almost completely destroyed but that any edematous swelling resulting from operative trauma was insufficient to cause obstruction.

The marked reduction of sphincteric function is best exemplified in eight dogs in which endocholedochal section was performed from three to six months after cholecystectomy. The average resistance in these animals was 90 mm. of water. Irritation of the papilla caused only a slight rise in the resistance, averaging 111 mm. of water. As previously stated, measurements of the resistance to the passage of fluid from the common bile duct into the duodenum represent the action of the entire sphincteric mechanism. This includes the muscle of Oddi and the effect produced by duodenal tonus acting on the common bile duct as it passes obliquely through the wall. Sphincterotomy as performed in these experiments divides the muscle of Oddi. The residual resistance of the sphincteric mechanism may be ascribed to the other aforementioned factors. The net result of sphincterotomy was to reduce markedly the ability of the sphincteric mechanism to go into spasm on irritation and, in addition, to cause a permanent reduction in its resistance.

The effect of cholecystectomy alone on dilatation of the biliary tract was noted in twenty animals. No dilatation of the duct was observed in twelve dogs at periods varying from one to six months. The ducts were dilated in eight dogs. This dilatation was seen in three of these animals in six months, in three in two months and in two in one month after cholecystectomy. Dilatation of the duct occurred only twice in a series of twelve animals in which both cholecystectomy and sphincterotomy were performed. Moreover, section of the sphincter in four animals in which dilatation of the duct was present after cholecystectomy resulted in the shrinkage of the ducts to normal diameter. It seems reasonable to assume that section of the sphincter appreciably reduces the incidence of dilatation of the biliary tract after cholecystectomy.

Endocholedochal sphincterotomy in the absence of the gallbladder was not followed by ascending infection. The slight round cell infiltration noted in the common duct in some animals and the periportal round cell infiltration found in the liver were similar to that observed in normal animals and in those that had undergone cholecystectomy. Cultures of bile from the common duct of many animals after combined cholecystectomy and sphincterotomy were sterile. The severe infection of the gallbladder, acute cholangitis and widespread perichol-

angitic abscesses noted by Mallet-Guy, Auger and Billa<sup>27</sup> in some animals in which the sphincter was cut by the transduodenal route were not found in this series. The three animals in which the gallbladder was left intact after sphincterotomy showed the presence of severe infection of the gallbladder and bile ducts. Whether this was due to an ascending infection or to one descending from the gallbladder as a result of puncture and manipulation of that organ could not be determined.

#### CONCLUSIONS

An instrument is described which safely divides the sphincter of Oddi through the common bile duct.

This method of sphincterotomy results in marked reduction of the function of the sphincteric mechanism.

Endocholedochal sphincterotomy in the absence of the gallbladder is not followed by ascending infection of the biliary tract.

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27. Mallet-Guy, P.; Auger, L., and Billa, M.: *Etat bactériologique des voies biliaires après section expérimentale du sphincter d'Oddi*, *Compt. rend. Soc. de biol.* **112**:899 (March 10) 1933.

# FAT EMBOLISM

## AN EXPERIMENTAL STUDY ON THE VALUE OF ROENTGENOGRAMS OF THE CHEST IN DIAGNOSIS

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The history of experimental fat embolism dates as far back as 1669, when Lower<sup>1</sup> did some work on lipemia and its effect on the circulation in animals. Since that time a tremendous amount of work has been done,<sup>2</sup> both clinically and experimentally, on the accurate detection of fat embolism. As far as we know, roentgen examination has never been used for this purpose. Therefore we are presenting for the first time the results of experimental work which show the value of the roentgenograms of the chest in the diagnosis of fat embolism.

### EXPERIMENTAL PROCEDURE AND RESULTS

We used eleven dogs in our experiments, selecting whenever possible an animal weighing close to 12.5 Kg. Sterile oleic acid was given intravenously to six animals and sterile olive oil to five. Doses of varying amounts were used in each experiment.

Owing to the researches of Landois,<sup>3</sup> who found that olein was the largest component of the fat of bone marrow, it was decided to try both oleic acid and olive oil in our experiments. The former, being the acid of the tri-oleate and easily obtainable, was used first. However, as it is toxic and probably unites with the alkaline radicals in the blood stream to form a soap, in the chemical sense of the term, olive oil, which is neutral and nontoxic in small quantities, was used as a control. It was found that 0.33 cc. of oleic acid per kilogram of body weight was sufficient to produce death in dogs, while 2.2 cc. of olive oil per kilogram of body weight was required.<sup>4</sup> The physical properties of the two substances were similar in that their viscosity was nearly equal and they produced similar droplets when emulsified.

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1. Lower, cited by Flournoy: *Contribution à l'étude de l'embolie graisseuse*, Paris, J.-B. Baillière & fils, 1878.

2. For a recent bibliographic review on this subject one may refer to Scuderi, C. S.: *Internat. Digest* **18**:195-215 (Oct.) 1934.

3. Landois, F.: *Fat Embolism*, *Deutsche med. Wchnschr.* **52**:283-285 (Feb. 12) 1926.

4. Fuchsig, cited by Warthin, A. S.: *Traumatic Lipaemia and Fatty Embolism*, *Internat. Clin.* **4**:171-227, 1913.



Fig. 1.—*A*, the normal pulmonary fields of a dog weighing 12.5 Kg., taken 28 inches (71 cm.) from the tube, 62 kilovolts, 30 milliamperes and an exposure of one-eighth second being employed. *B*, the pulmonary fields of the same dog twenty minutes after the intravenous injection of 6 cc. of sterile oleic acid. The same technic was used. Note the diffuse cloudiness of the pulmonary fields.

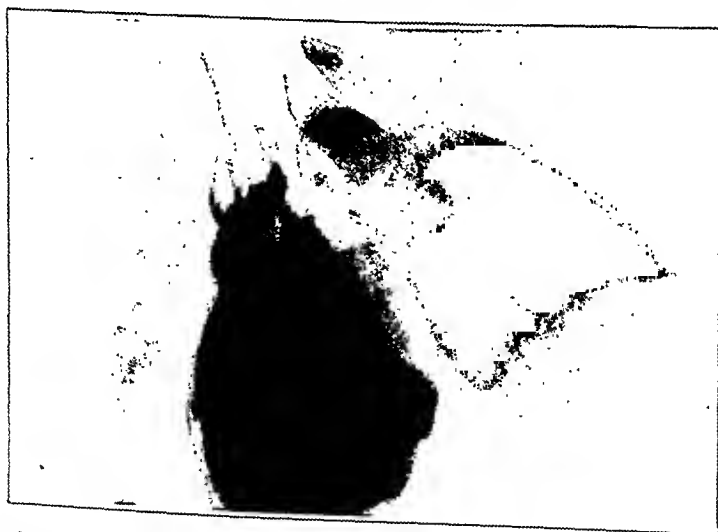


Fig. 2.—A roentgenogram of the thoracic organs of the dog used for figure 1 after the death of the animal. The organs were removed from the thoracic cavity to show better the detail. One readily notes the apparent hepatization of the pulmonary tissue, even in the roentgenogram.

First the technic for making roentgenograms of the chest of a dog had to be worked out. Once the plates began to be uniformly good, the oily substances were injected. By taking pictures before and after the injections we were able to compare the pulmonary fields, taken in each instance with the same technic.

Figure 1*A* shows the normal pulmonary fields of one of the animals. The lungs were relatively clear, except for the usual clouding at the hilus. Figure 1*B*, was taken twenty minutes after the injection of 6 cc. of sterile oleic acid. There was more or less cloudiness of a diffuse, even nature in the pulmonary fields. No patches or areas of increased opacity were noted. The heart showed no enlargement when measured by superimposition of the films. The next morn-

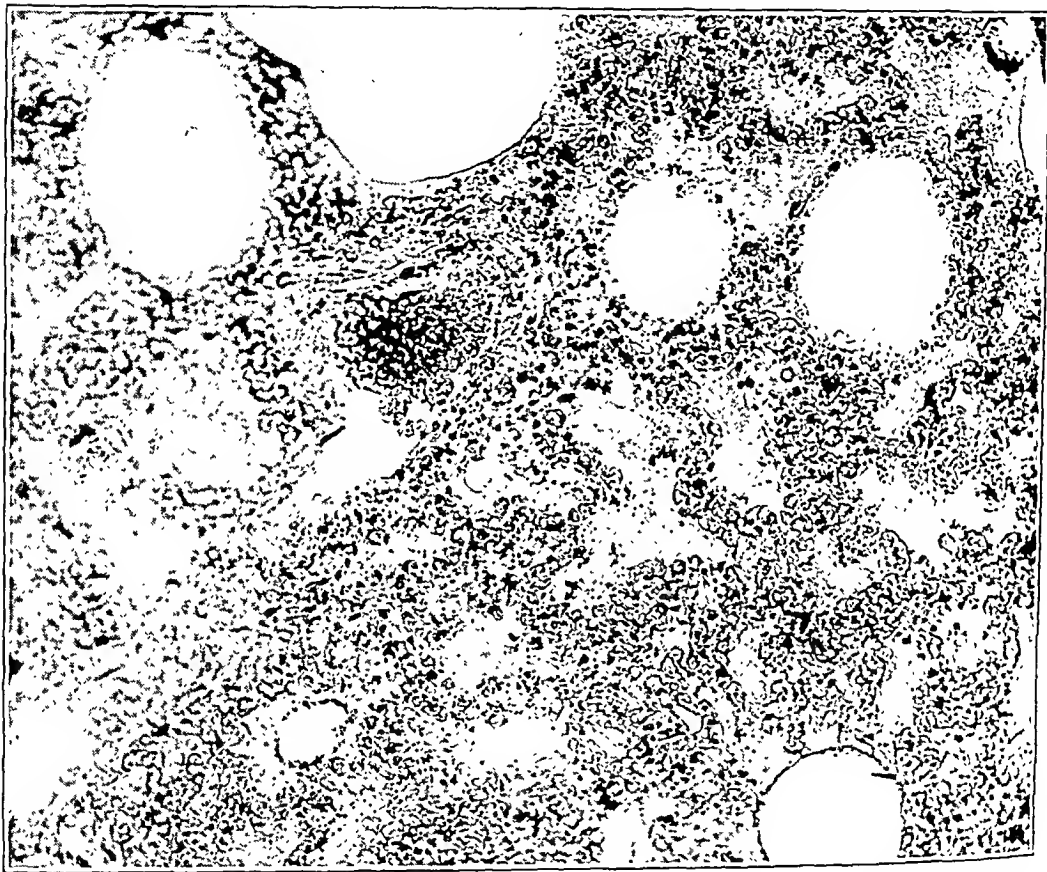


Fig. 3.—Microscopic section of the lung, stained with sudan III. The animal received 6 cc. of sterile oleic acid intravenously prior to its death. Note the plugged vessel in the center of the field and some of the darkly stained fat droplets in the epithelial cells and alveoli. The linings of the alveoli are markedly edematous, showing the effect of the interference with the circulation. Note also the alveoli partially filled with serous exudate.

ing the dog was found dead, rigor mortis being present. The thoracic organs were removed, and a roentgenogram was made of them *in toto*. There was a lack of air in the lungs (fig. 2). The appearance of the lungs on gross examination and on cut section simulated liver or the hepatization found in cases of bilateral pneumonia. Palpation revealed no crepitant areas.



Fig. 4.—*A*, the normal pulmonary fields of the second experimental animal before the injection of oleic acid. The picture was taken at 28 inches, 62 kilovolts, 30 milliamperes and an exposure of one-eighth second being used. This dog weighed 8 Kg. *B*, the pulmonary fields of the same animal taken twenty-five hours after the intravenous injection of 2 cc. of sterile oleic acid. The same technic was used for both roentgenograms. Note the diffuse hazy cloudiness in the pulmonary fields. The animal was perfectly well and happy at the time the picture was made. No ill effects were noted.



Fig. 5.—*A*, the normal pulmonary fields of a dog weighing 13 Kg. This picture was made 36 inches (91 cc.) from the tube, 64 kilovolts, 100 milliamperes and an exposure of one-tenth second being used. *B*, the pulmonary fields of the same animal photographed with the same technic forty-eight hours after the intravenous injection of 10 cc. of sterile olive oil. Note the same diffuse cloudiness of the upper part of both pulmonary fields. This feature was present in all our animals.



Microscopic sections were made (fig. 3) and examined by Dr. Benjamin Neiman of the department of pathology of the Cook County Hospital. Dr. Neiman described the appearance of the lungs as being typical of that of a drowned animal, owing to the marked edema of the epithelial cells lining the alveoli and to the fact that clear serums filled the alveoli. Sections stained with sudan III readily showed the fat-filled capillaries.

Figure 4 *A* shows the pulmonary fields of a second animal prior to any experimentation. Twenty-five hours after the injection of 2 cc. of sterile oleic acid, another roentgenogram was made (fig. 4 *B*). The animal at that time appeared perfectly happy and normal in every respect. The technic used in taking the two pictures was identical. Close examination revealed the same diffuse haziness of the pulmonary fields as was seen in figure 1 *B*.

Figure 5 *A* shows the normal pulmonary fields of a third experimental animal. Ten cubic centimeters of sterile olive oil was injected intravenously, and forty-eight hours later another roentgenogram was made (fig. 5 *B*). The same diffuse cloudiness of the pulmonary fields, so characteristically found in all the experiments, was likewise present. The upper lobes show the pathologic process clearly.

From 2 to 12 cc. of oleic acid was injected into six animals, while from 2 to 20 cc. of olive oil was injected into five.

The animals receiving less than the lethal dose of oleic acid (4 cc.) showed evidence of pulmonary irritation for several days. Each of these animals had an apparent cold, with periodic sniffing and coughing, but otherwise they appeared to be normal.

The animals receiving up to 20 cc. of sterile olive oil showed no evidence whatsoever of any pulmonary irritation or malaise and suffered no apparent ill effects from the experiment. One of the animals after receiving 20 cc. of olive oil became ataxic and had great difficulty in controlling the extremities, although otherwise it appeared normal. The ataxic state lasted about ten minutes, after which the dog ran around and appeared to be normal. This period was probably due to interference with the cranial circulation by the fat droplets.

#### COMMENT

One must not lose sight of the fact that fat embolism is not a true embolism in the sense of a permanent occlusion of a vessel but is simply a retardation of the blood flow through a capillary while the oil droplets become elongated and are slowly forced from the arteries to the veins. Gauss<sup>5</sup> showed that the addition of 1 part of olive oil to 9 parts of the serum of human beings increased the viscosity of the mixture approximately three times.

The production of pathologic changes in the lungs of experimental animals after intratracheal insufflation of various oils has been nicely worked out by Pinkerton,<sup>6</sup> while Lehman and McNattin<sup>7</sup> have done a

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5. Gauss, H.: Studies in Cerebral Fat Embolism, *Arch. Int. Med.* **18**:76-102 (July) 1916.

6. Pinkerton, Henry: The Reaction to Oils and Fats in the Lungs, *Arch. Path.* **5**:380-401 (March) 1928.

7. Lehman, E. P., and McNattin, R. F.: *South. M. J.* **22**:201-207 (March) 1929.

commendable piece of work on the pathologic changes in the lungs of dogs after the intravenous injection of cottonseed oil, cod liver oil, liquid petrolatum and iodized poppy-seed oil 40 per cent. They have produced permanent pathologic changes in the lung from one hour to five hundred and seventy-two days after the injection of 1.2 cc. of cottonseed oil per kilogram of body weight. We feel that little can be added to this phase of the problem which has been so completely worked out, and for this reason we have not delved into the pathologic study further.

#### CONCLUSIONS

In dogs 0.16 cc. of oleic acid or of olive oil per kilogram of body weight is sufficient to produce changes in the pulmonary fields that may be visualized roentgenographically.

These changes can be demonstrated for from five to seven days after the injection and as shortly as twenty minutes after the oil has been placed in the blood stream.

A diffuse haziness or cloudiness of the pulmonary fields has been persistently present in all our experimental animals.

The uniformity of our results makes us feel that fat droplets in the pulmonary circulation, if present in sufficient number, will always produce changes in the pulmonary fields that are detectable in roentgenograms.

From the results of our experiments, we believe that roentgenograms of patients suffering from clinical fat embolism should be of definite diagnostic aid. Further study on human beings will be undertaken whenever the opportunity occurs.

Dr. C. Warfield, head of the Department of Roentgenology of the Cook County Hospital, cooperated with us in the technical work of this study.

# PRIMARY STREPTOCOCCIC PERITONITIS

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The etiology of diffuse peritonitis in children differs from that usually seen later in life. The source of infection is frequently extra-abdominal; the attending sepsis so often dominates the clinical picture that the peritonitis may be temporarily overlooked. Metastatic peritonitis due to hemolytic streptococci is more common than is usually acknowledged. The individual physician does not often recognize the pathologic process early because of his limited experience with this entity. While this discussion is concerned primarily with streptococcic peritonitis in children, the forms which occur in adults are included to complete the study.

The diagnosis of the acute forms of peritonitis is difficult in childhood and more particularly in infancy. The reason lies in an inability to obtain an accurate subjective history, the difficulty in making a reliable physical examination and the frequency with which irregular complaints referable to the abdomen accompany infections of the upper respiratory tract, gastro-intestinal upsets and acute infectious diseases in young children. As a result of a tendency to minimize or ignore abdominal discomfort under these conditions, advanced peritonitis not infrequently exists by the time a child is brought to the hospital. Until recent years, primary streptococcic peritonitis was considered a rare and inevitably fatal disease. A comprehensive study of a large series of cases has led to the conclusion that this entity can be more easily recognized than is generally believed and that there is a logical form of treatment.

Primary streptococcic peritonitis is especially a disease of infancy and childhood but may occur in adult life. In the last eleven years there were forty-two certified cases under observation in the Mount Sinai Hospital. Not included in this group are instances of peritonitis following trauma, perforation of a viscus and *Durchwanderungs* peritonitis secondary to infection or ulceration of the gastro-intestinal tract. The peritoneal exudate in all the cases in this series revealed *Streptococcus haemolyticus* (beta) on culture, the fluid being obtained by puncture, at operation or at autopsy.

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## CHARACTERISTIC PICTURE OF STREPTOCOCCIC PERITONITIS

The history, while characteristic, is not definitely pathognomonic of the disease. An example follows:

A 9 month old boy during a winter month had an attack of moderately acute pharyngitis, with a temperature of about 101 F., which subsided in two days. After an interim of three or four days, during which the child seemed to have recovered, there was a sudden recrudescence of fever, the temperature often rising to 103 F., accompanied by fretfulness and anorexia. For lack of definite findings these symptoms at first were attributed to an obscure otitis media, but after a day abdominal enlargement occurred, followed by constant generalized abdominal pain which was not overly severe. The child seemed to have a marked indefinable infection, vomiting some of its food and passing infrequent greenish, watery stools. In several days, during which he was treated for a gastro-intestinal upset, the condition became progressively worse, the spiked afternoon temperature of 103 F. falling to 100 or 101 F. in the morning. At last, the progressive abdominal distention and the marked general illness brought the patient to the hospital.

On admission, the infant, though well nourished, appeared semimoribund, with a hippocratic facies. The skin was dry and clear, the throat was moderately reddened and one ear drum was slightly injected. The respiratory rate was 36 per minute, and there was evidence of pneumonia. The pulse was weak, with a rate of 140 per minute; the heart sounds were clear. The abdomen had a diffuse, somewhat tense enlargement with generalized tenderness to moderate pressure; no rigidity or masses were felt. The spleen was just palpable, and some shifting dullness was present. The umbilicus was pouting and slightly reddened. Laboratory examination revealed a few pus cells in the urine and a leukocyte count of 26,000, with 94 per cent neutrophils and 6 per cent lymphocytes.

In a case of this type the diagnosis and question of operation must be determined immediately, the possibilities being pneumonia with reflex meteorism, acute enteritis and peritonitis due to appendicitis or peritonitis of the acute serous, pneumococcic or streptococcic type. The pathologic process in the chest is not marked enough to explain the sepsis; the distention and tenderness are too prominent to be due to reflex ileus. The possibility of appendicitis with generalized peritonitis is in the foreground. However, the early general tympanites and pain, with the absence of localization to the lower right quadrant, the high leukocyte count, the relatively mild nausea and vomiting and the age of the patient are not the typical picture of this condition.

Gastro-enteritis usually produces more troublesome vomiting, diarrhea and cramps, with a lower leukocyte count. Enteritis is more common in the summer and does not cause the prominent distention and toxemia, except as a terminal manifestation. The possible diagnoses of acute serous, pneumococcic or streptococcic peritonitis cannot be absolutely differentiated by the subjective findings. For a positive determination, abdominal puncture is performed close to the umbilicus in the lower left quadrant. A few drops of odorless cloudy yellowish green exudate are obtained, which indicates merely that peritonitis is present. On smear, many pus cells and scattered gram-positive cocci in

short chains are found. This is pathognomonic of streptococcic peritonitis. The exudate and blood ultimately yield pure cultures of *Str. haemolyticus* (beta).

However, in cases of streptococcic peritonitis, the abdominal symptoms are not always urgent, sometimes being so insignificant that attention is not directed to them. Because of the lack of complaints referable to the abdomen, the tympanites often is completely overlooked until the patient is hospitalized. In this type, pain and distention are slight, and either one may be absent. No fluid wave is recognized, and there is slight tenderness to pressure all over the abdomen. The flat abdomen does not necessarily indicate the absence of a peritoneal exudate, for in these instances as much fluid may be present as in the meteoric type. Supported by a history of preceding infection of the upper respiratory tract, followed by a sudden exacerbation of fever several days later, peritonitis must be suspected when the child appears to be too ill for the symptoms to be attributed to the respiratory condition. Peritoneal puncture here is an invaluable aid in determining the diagnosis.

Analysis of the cases at the Mount Sinai Hospital shows that primary streptococcic peritonitis occurs most frequently in childhood, involving the sexes equally. Half of the females and three fourths of the males were under 18 months of age, with an average age of 8 months. The condition was most common during the cold season, one half of the cases occurring during the winter and one fourth during the early spring. In 60 per cent, there had been a definite preceding pharyngitis. In only six could no possible source of infection be determined. The usual triad is infection of the respiratory tract, abdominal involvement and sepsis. The acute pharyngitis usually occurred within a week of admission to the hospital and often was not marked. The fever was initiated in six patients by a sensation of chilliness, the temperature ranging from 101 to 104 F. Commonly, the initial sore throat and fever had subsided before abdominal discomfort started from two to three days later, the temperature again rising with the onset of the latter. Distention was usually the first abdominal sign in most patients, and in half of them vomiting occurred. Diarrhea, with greenish, watery stools, which occurred in a third of the patients, was not characteristic, and no blood was noted in the discharge. Several of the patients were constipated for a few days. Abdominal pain occurred in a fourth of the patients; it developed with the distention and was constant and usually generalized; it often decreased or disappeared after several days. Rigidity of the rectus muscles was rarely seen.

The severity of illness was not influenced by the physical development of the patients, for the majority of them were well nourished and well developed. Examination of the throat often showed the remains of the antecedent pharyngitis, but sometimes the throat appeared to be

normal. Cervical adenopathy was occasionally felt. The abdomen was diffusely enlarged and tender in the majority of instances, although a soft fulness was not uncommon. There was no muscular spasm or especial localization of complaints. Evidence of fluid was sometimes elicited.

#### ABDOMINAL PUNCTURE AND CULTURE OF FLUID

An invaluable aid in diagnosis was abdominal puncture, as described by Neuhof and Cohen.<sup>1</sup> Puncture was performed on thirty patients, yielding conclusive evidence of the underlying pathologic process in all.

Paracentesis is usually performed just below the level of the umbilicus to either side of the midline, but it may be done through or lateral to the rectus muscle. Needless to say, this should not be attempted over a solid organ or a palpable or questionable mass. The skin is prepared with iodine, and a small wheal is made with procaine hydrochloride. A little incision may be made in the skin to preserve the delicacy of touch when the needle is introduced. A lumbar puncture needle and a well fitting 20 cc. syringe are used. The needle with stylet in place is introduced perpendicularly, with slow, even pressure. In puncturing through the rectus muscle, the resistance of the anterior sheath is felt. As the needle passes through the muscle, a similar resistance of the posterior sheath is encountered, and then the needle enters the peritoneal cavity. The stylet is withdrawn and the syringe attached. While gentle suction is maintained, the needle is pointed in various directions, being left in position for several minutes to permit recognition of small amounts of fluid. Care must be taken, for when only a thin film of exudate lies under the anterior parietal portion of the peritoneum the aspirated fluid may fill only the needle and not appear in the syringe. Therefore, suction should be continued as the needle is withdrawn. Contrary to the opinion of others, I have found this to be a safe procedure and have never injured or penetrated the bowel. The quantity of fluid aspirated does not necessarily parallel the amount assumed to exist in the peritoneal cavity. The Denzer trocar-cannula<sup>2</sup> is sometimes used for abdominal puncture. After this is inserted into the peritoneum, the trocar is withdrawn and a fine glass capillary tube is introduced to extend 2 mm. beyond the end of the cannula. The capillary attraction of the glass is said to reveal fluid when small quantities, as low as from 7 to 10 cc., are present. The fluid is smeared and stained by the Gram technic. It is thin, odorless, turbid and yellowish or greenish.

All the specimens of fluid obtained on paracentesis yielded pure cultures of *Str. haemolyticus* (beta), with the exception of one which yielded *Str. viridans* (alpha) and another in which were found a few colonies of *Bacillus coli* mixed with the predominating hemolytic streptococci. All of the fluids had gram-positive cocci in short chains with many polymorphonuclear cells; in only one were the pus cells absent. The peritoneal exudate often showed a positive reaction as early as the first day of peritoneal involvement.

1. Neuhof, H., and Cohen, I.: Abdominal Puncture in the Diagnosis of Acute Intraperitoneal Disease, *Ann. Surg.* 83:454, 1926.

2. Denzer, R. S.: The Diagnosis of Peritonitis and Peritoneal Transudates in Infants by Means of Abdominal Puncture with the Capillary Tube, *Am. J. M. Sc.* 163:237, 1922.

Specimens of blood were taken in twenty-three cases; on culture, eight showed pure growths of *Str. haemolyticus* (beta), ranging from 15 to 450 colonies per cubic centimeter; fifteen were sterile, and one showed *Str. viridans* (alpha), the same as in the peritoneal fluid. Most of the cultures were made within thirty-six hours of admission, about from three to five days after the onset of the illness. The leukocyte count was elevated, ranging from 14,000 to 60,000, and averaging 22,000, with about 95 per cent neutrophils.

The following technic, developed by Dr. Gregory Shwartzman, has been used for blood cultures in the last seven years:

The freshly drawn blood is inoculated into the mediums at the bedside. Two cubic centimeters of blood is placed in tubes containing, respectively, dextrose agar and semisolid medium (dextrose broth, agar and chopped beef) and in a tube containing an anaerobic medium (liver in dextrose broth). Five cubic centimeters of blood is put into flasks containing, respectively, tomato extract-dextrose broth, dextrose broth and plain broth. At the end of twenty-four hours, smears are made of the specimens in all suspicious flasks. The clear mediums are each inoculated into a tube containing ascitic agar slant and one containing dextrose broth. This procedure is repeated on the second day.

The peritoneal fluid is cultured on dextrose broth, on anaerobic liver broth and on plates of the medium of Endo, plain agar, blood agar and ascitic fluid agar. Hemolytic colonies are all inoculated into esculin mediums (esculin, sodium taurocholate, peptone and ferric sulfate). The beta hemolytic streptococcus has no effect on this, while the hemolytic enterococcus turns the mediums black in a day.

#### THERAPY

Those patients who were first seen in a prostrated condition had an unfavorable prognosis. The marked septic condition so dominated the syndrome that any early operative procedure was definitely contraindicated. Unfortunately, no panacea was found, each case being a problem unto itself. In view of the high mortality, various types of management were tried. Supportive treatment was important in all. The patients were placed in a high Fowler position and given continuous intravenous drips of 5 per cent dextrose in saline or in Ringer's solution. A transfusion of from 50 to 225 cc. of citrated blood or of normal human serum was given every two or three days. Intravenous injections of pooled antistreptococcus serum or mercurochrome were sometimes used as adjuncts, but they gave no consistently beneficial results. The temperature rose to 103 F., with a decrease in the morning to 100 F.; in a fourth of the cases there was a terminal pyrexia with a temperature of 107 F. Sponge baths with alcohol were freely used for the patients' comfort. Often the meteorism increased, and paralytic ileus with gastric retention set in, requiring gastric lavage. For local treatment, heat may be applied, but cold is preferred. The use of ice bags or the Leiter coil is efficacious. As aids in relieving distention, suppositories of glycerin, turpentine stupes and the administration of

physostigmine or of small doses of posterior pituitary may be repeated every three hours.

Feeding of children was often a problem. When no gastric retention was present, liquid and soft diets were given with impunity. When regurgitation occurred, gastric lavage before feedings often helped in keeping the food down. Even though distention and fever were present, food was given by mouth to the cooperative patients.

In those having mild sepsis with evidence of much peritoneal exudate, clinical relief was sometimes obtained by abdominal drainage performed by the most expedient method. This was done either by repeated aspiration or by the temporary insertion of a catheter into the enlarged paracentesis track. In one patient who recovered, small drains purposely inserted in each inguinal region yielded more than 136 ounces (4,080 cc.) of pus before the opening was closed. Encapsulation of the peritoneal exudate occurred about two weeks after the onset of peritoneal symptoms. Localization of infection was attended by general improvement, so that drainage could then be performed with safety. Often small exudates felt only by rectal examination eventually resolved spontaneously. Encapsulation was recognized by palpation of an abdominal tumor rather than by the character of the pus, for in the later stage the exudate is only slightly thicker than at first.

Of the complications, bronchopneumonia alone or combined with pleural exudation was the most common. Its presence did not necessarily elevate the temperature or increase the leukocyte count. Thoracentesis was performed as often as necessary to control respiratory or cardiac embarrassment. The urinary output was satisfactory, and laboratory examination revealed evidence of acute nephritis in only three patients. Meningeal irritation was present in only two cases. In three patients who recovered scattered abscesses of the skin or bone developed during their long convalescence. When death occurred, it was due to an overwhelming sepsis. All of the patients who recovered were seen at various intervals after discharge and were found to be quite well and symptomless.

Nine patients recovered. Six were treated surgically and three medically. Of the latter, one had a small catheter inserted for several hours through the enlarged paracentesis opening. Of those treated surgically, two had operation postponed until definite localization occurred, the abscess then being drained. Appendectomy with drainage was performed on two patients, and two more had abdominal drains inserted without anything more being done.

#### POSTMORTEM OBSERVATIONS

Autopsy was performed in twenty-one of thirty-three fatal cases. There was no relation between the severity of the peritoneal pathologic process and the duration and severity of the illness. The abdomen



Sex	Age	Date of Admission	Time in Hospital	Diagnosis on Admission	Preceding Infection (Days Before Admission)	Temperature (Days Before Admission)	Vomiting	Abdominal Distention	Bowel Habits	Leukocytosis
F	10 yr.	March 1924	73 days	Osteomyelitis; streptococcal peritonitis	Pharyngitis 11 days 104 F.	102 F. 8 days with pain	2+ 8 days	4+ 7 days	Constipated	20,800
F	9 yr.	October 1924	4 days	Peritonitis, tuberculous or pneumococcal	Pneumonia 11 days	105 F. 7 days with pain	2+ 5 days	1+ 7 days	Diarrhea 3+ 5 days	21,100
	54 yr.	April 1925	2 days	Subacute pancreatitis	Pharyngitis 5 days 102 F.	104 F. 4 days with chills	0	1+ 4 days with pain	Constipated	16,100
F	6 mo.	March 1927	8 hr.	Peritonitis; meningitis	0	104 F. 3 days	2+ 1 day	3+ 3 days	Constipated	.....
M	9 mo.	March 1927	1 day	Pyelonephritis	0	104 F. 11 days	2+ 2 days	2+ 4 days	Diarrhea 1+ 1 day	17,900
M	6 mo.	June 1927	40 days	Peritonitis; pneumonia	Pharyngitis 5 days	103 F. 3 days	0	3+ 3 days	Diarrhea 1+ 1 day	20,100
M	2 mo.	January 1928	8 hr.	Peritonitis or intussusception	0	101 F. 3 days	2+ 3 days	2+ 3 days	.....	.....
M	15 mo.	February 1928	3 days	Primary peritonitis	Pharyngitis 1 wk.; otitis media 3 days	105 F. 7 days	2+ 2 days	2+ 2 days	Diarrhea 2+ 2 days	19,000
M	10 mo.	February 1928	3 days	Primary peritonitis; pneumonia	Pharyngitis 1 wk.	106 F. 4 days with chills	0	4+ 1 day	Constipated	11,500
M	1 mo.	April 1928	3 days	Primary peritonitis; sepsis	Pharyngitis 1 wk.	102 F. 7 days	0	4+ 1 day	Diarrhea 3+ 2 wk.	14,800
M	1 yr.	December 1928	10 hr.	Appendical peritonitis or adenitis	Pharyngitis 3 days	104 F. 10 days with a chill	0	3+ 3 days	.....	23,100
F	3 mo.	December 1928	1 day	Primary peritonitis	Pharyngitis 5 days	102 F. 5 days	0	3+ 1 day	Diarrhea 1+ 1 day	.....
M	2 mo.	February 1929	1 day	Primary peritonitis; paralytic ileus	Pharyngitis 9 days 101 F.	105 F. 5 days	1+ 1 day	1+ 1 day	.....	14,400
F	2 mo.	February 1929	3 days	Primary peritonitis; sepsis	Pharyngitis 2 wk.; bilateral otitis media 1 wk.	105 F. 5 days	0	3+ 5 days	Normal	13,700
M	6 mo.	March 1929	1 day	Primary peritonitis	Pharyngitis 6 days 103 F.	101 F. 4 days	0	3+ 4 days	Diarrhea 2+ 4 days	.....
F	2 wk.	May 1929	12 hr.	Peritonitis	Pharyngitis 4 days	102 F. 4 days	2+ 1 day	3+ 2 days	Diarrhea 2+ 4 days	.....

# Primary Streptococcic Peritonitis

	Culture of Fluid Obtained on Abdominal Puncture	Blood Culture (Days After Admission)	Operative Procedure	Operative Findings and Culture of Exudate	Clinical Observations and Developments	Results, (Recovery, Death or Autopsy)
	Str. haemolyticus (beta), first day	Str. haemolyticus (beta), tenth day	Tube drainage of lower left quadrant, second day	Generalized peritonitis; fine adhesions	Thoracotomy for effusion; Str. haemolyticus on culture; incision and drainage of multiple bone abscesses	Follow-up study; patient symptomless and well
	Str. haemolyticus (beta), lower right quadrant, first day	.....	Puncture drainage of epigastrium	.....	Ileus; accidental pneumothorax after thoracentesis	General peritonitis; Str. haemolyticus (beta) and Staph. aureus on culture; bronchopneumonia of right lung; left pneumothorax; B. coli and mixed streptococci on culture of vaginal discharge
	Str. haemolyticus (beta), upper left quadrant, first day	Negative, first day	Laparotomy; nothing done	Generalized bile-stained peritonitis	Toxic jaundice	General peritonitis; 500 cc. of pus; Str. haemolyticus (beta) on culture; splenomegaly; no source of infection found
	.....	.....	.....	.....	.....	General peritonitis; 30 cc. of pus; Str. haemolyticus (beta) on culture; mesenteric adenitis; brain normal; pure B. coli on culture of appendix
	Str. viridans	Negative, first day	.....	.....	.....	Died
	Str. haemolyticus (beta), first day	Negative, first and fourth days	Puncture drainage of lower left quadrant	.....	Drainage of small subcutaneous abscess on twenty-third day	Follow-up study; patient symptomless and well
	.....	.....	Laparotomy; nothing done	Generalized peritonitis; Str. haemolyticus (beta) on culture	Collapse; temperature to 105 F.	Died
	Str. haemolyticus (beta)	Negative, first day	.....	.....	Str. viridans on culture of material from throat	General peritonitis; bilateral bronchopneumonia; tonsils necrotic with thrombosis of vessels
	Str. viridans	Str. viridans	.....	.....	Erysipelas on face developed on first day	General peritonitis; 50 cc. of pus; Str. haemolyticus (beta) on culture; bronchopneumonia and pleurisy; esophagitis
	Str. haemolyticus (beta), lower left quadrant, first day	Str. haemolyticus (beta), first day	.....	.....	Collapse	General peritonitis; Str. haemolyticus (beta) and B. coli on culture; bronchopneumonia of upper lobe of right lung
	Str. haemolyticus (beta), first day	Negative, first day	.....	.....	Extreme distention with temperature to 107 F.	General peritonitis; Str. haemolyticus (beta) on culture; edema of ascending colon; mesenteric adenopathy; abscesses of tonsils; splenomegaly
	Str. haemolyticus (beta), first day	Negative, first day	.....	.....	Umbilicus red; temperature up to 104 F.	Died
	.....	.....	.....	.....	Moribund on admission; umbilicus red and pouting	General peritonitis; 240 cc. of fluid; Str. haemolyticus (beta) and few B. coli on culture; bronchopneumonia; abscesses of tonsils
	Str. haemolyticus (beta), second day	.....	.....	.....	Moribund on admission	General peritonitis; 300 cc. of pus; purulent otitis media; splenomegaly
	Str. haemolyticus (beta), first day	.....	.....	.....	Moribund on admission; umbilicus red and pouting	General peritonitis; 100 cc. of pus; multiple abscesses of the lung; mesenteric adenitis; acute tonsillitis
	Str. haemolyticus (beta)	.....	.....	.....	Moribund on admission	General peritonitis; 200 cc. of fluid; Str. haemolyticus (beta) on culture; mesenteric adenitis; purulent hepatitis

*Data in Forty-Two Cases of Primary*

Sex	Age	Date of Admission	Time in Hospital	Diagnosis on Admission	Preceding Infection (Days Before Admission)	Temperature (Days Before Admission)	Vomiting	Abdominal Distention	Bowel Habits	Leukocytes
F	1 mo.	March 1933	6 days	Erysipelas of chest	Erysipelas of chest 2 days	101 F. 4 days	0	0	.....	18,000
M	2 mo.	April 1933	7 days	Erysipelas of cheek	Pharyngitis and otitis media 6 days	102 F. 3 days	0	2+ 1 day	.....	33,400
F	4 yr.	July 1933	1 day	Primary peritonitis; tonsillitis	Pharyngitis 4 days	102 F. 4 days	0	1+ with pain 2 days	Diarrhea 4+ 3 days	26,000
F	3 yr.	October 1933	1 day	Primary peritonitis; sepsis	Cough and otitis media 3 days	104 F. 3 days	2+ with pain 2 days	4+ 2 days	Constipated	.....
M	1 yr.	March 1934	2 days	Primary peritonitis; sepsis	Otitis media 2 wk. 106 F.	104 F. 7 days	2+ 1 day	2+ 4 days	.....	17,000
M	6 mo.	March 1934	2 days	Primary peritonitis; pneumonia	Pneumonia 5 days	102 F. 5 days	2+ 3 days	4+ 3 days	0	15,000
F	32 yr.	April 1934	3 mo.	Peritonitis	Pharyngitis 6 days	103 F. 1 day	0	0 pain 1 day	0	33,100
M	4 yr.	April 1934	4 wk.	Peritonitis; pleurisy; tonsillitis	Pharyngitis and otitis media 6 days	103 F. and chilliness 6 days	2+ 2 days	3+ and pain 2 days	Diarrhea 1+ 1 day	37,700
F	5 yr.	May 1934	4 days	Pyelitis; perinephritic abscess (?)	Pharyngitis 3 wk.	104 F. 10 days	0	1+ 3 days	.....	34,000
F	11 yr.	February 1935	2 mo.	Primary peritonitis	Pharyngitis 10 days	104 F. 3 days	4+ 3 days	0	.....	25,000
F	6½ yr.	February 1935	6 wk.	Sepsis	Pharyngitis 5 days	102 F. 5 days	0	2+ 2 days	0	27,000
M	1½ yr.	February 1935	23 days	Peritonitis	Pharyngitis 1 wk.	103 F. 4 days	2+ 4 days	0	0	27,000
F	40 yr.	May 1935	1 mo.	Ruptured appendix (?)	0	103 F. 7 days	0	2+ with pain 6 days	Diarrhea 2+ 7 days	10,000

*Streptococcic Peritonitis—Continued*

Culture of Fluid Obtained on Abdominal Puncture	Blood Culture (Days After Admission)	Operative Procedure	Operative Findings and Culture of Exudate	Clinical Observations and Developments	Results (Recovery, Death or Autopsy)
.....	.....	.....	.....	Erysipelas spread to whole torso on sixth day developing 3+ distention	General peritonitis; 50 cc. of fluid; Str. haemolyticus (beta) on culture; atelectasis; patent foramen ovale
Str. haemolyticus (beta), seventh day	.....	.....	.....	Jaundice with spreading of erysipelas developed on seventh day	Died
Str. haemolyticus (beta), lower right quadrant	Str. haemolyticus (beta)	.....	.....	Str. haemolyticus (beta) on culture of material from throat; chill with temperature of 106 F. on admission	Died
Str. haemolyticus (beta) and few B. coli	Str. haemolyticus (beta)	.....	.....	.....	General peritonitis; 250 cc. of fluid; Str. haemolyticus (beta) on culture; bilateral pleurisy; acute nephritis (medical)
Str. haemolyticus (beta)	Negative	.....	.....	Marked distention and vomiting developed; umbilicus reddened	Died
Str. haemolyticus (beta), lower left quadrant, first day	.....	.....	.....	Green watery diarrhea developed in hospital	General peritonitis; 500 cc. of pus; confluent bronchopneumonia; mesenteric adenopathy
Str. haemolyticus (beta), first and second days	Negative, first and second days	Drainage of pelvic abscess after 2 months' hospitalization	Large amount of pus in cul-de-sac; Str. haemolyticus (beta) on culture	Pleural effusion developed on right side; Str. haemolyticus (beta), Staph. albus, and diphtheroids on culture of material from throat	Follow-up study; patient symptomless and well
Negative, first day; Str. haemolyticus (beta), lower left quadrant, second day	Negative, first day	Drainage of pelvic abscess after 17 days in hospital	Large amount of pus above bladder; Str. haemolyticus (beta) and Staph. albus on culture	Str. haemolyticus (beta) on culture of material from throat; ileus developed after operation; very ill	Follow-up study; patient symptomless and well; except for slight incisional hernia
Str. haemolyticus (beta), lower left quadrant, third day	Negative, third day	.....	.....	Distention, vomiting, and diarrhea developed on second day in hospital	General peritonitis; left retro-peritoneal phlegmon; embolic abscesses of jejunum; fibrinous pleuritis; bronchopneumonia
Str. haemolyticus (beta), first day	Negative, second day	.....	.....	.....	Follow-up study; patient symptomless and well
Str. haemolyticus (beta), first and third days	Negative, third day	Drainage of abdominal pus by bilateral inguinal incisions on second day	Large amount of pus and general peritonitis; many adhesions seen	Required two drainages of left pleural effusions; large amount of pus drained from chest and abdomen	Follow-up study; patient symptomless and well
Str. haemolyticus (beta), lower right quadrant, first day	Str. haemolyticus (beta), first day	.....	.....	Abscess of buttock drained; Staph. aureus on culture	Follow-up study; patient symptomless and well
.....	.....	Appendectomy and drainage	General peritonitis; terminal ileum and mesentery thickened; Str. haemolyticus (beta) on culture	Ileus developed for 4 days after operation	Follow-up study; patient symptomless and well

was distended as a result of intestinal paralysis and the peritoneal exudate. The fluid was odorless, thin, turbid and yellowish or green and varied in quantity from 200 to 1,100 cc. Often the larger amounts were found in small children showing slight tympanites. The peritoneum was diffusely reddened, granular and frequently covered with small fibrinous plaques. Sometimes there were weblike strands between loops of bowel. The pus had no interintestinal loculations but lay free beneath the parietal peritoneum. There was no indication that the infection had started or had been especially severe in any one part of the abdomen. Several of the females had had a slight vaginal discharge, but examination revealed no evidence that the peritoneum had been involved through an ascending genital infection. In none of the thirteen females was there inflammation of the mucosa of the uterine tube. In five cases in which there was a pouting reddened umbilicus before death, no evidence of omphalitis was discovered at autopsy. The major pathologic changes were: fibrinopurulent peritonitis, twenty-one cases—pure cultures of hemolytic streptococcus, twelve; no culture, five, and a few colon bacilli mixed with the predominating beta hemolytic streptococcus, four—mesenteric adenopathy, six; bronchopneumonia, seven; pneumonia with pleurisy, three; pleurisy alone, three; atelectasis, four; acute or necrotizing tonsillitis, five; otitis media, eleven, and erysipelas, three. Cultures of some mesenteric glands were sterile. The few colon bacilli present in the peritoneal exudate were thought due to postmortem contamination.

Whether the bronchopneumonia preceded or followed the peritonitis can only be surmised. It is well known that bacteria from the abdomen can easily pass through the central tendon of the diaphragm to reach the pleural cavity and that they can pass in either direction through the diaphragm. There was no especial accentuation of subphrenic inflammation to indicate that the peritoneum had been involved by continuity. The atelectasis and basilar pneumonia were probably due to the fixation and elevation of the diaphragm by the meteorism.

Sections were made of all organs, especially of the intestines. There was infiltration of the serosa in eight cases, showing many polymorphonuclear cells with gram-positive cocci. This extended to the subserosa in one case and to the muscle layer in another. A similar picture was seen in all of the appendixes removed at autopsy or at operation. The mucosa nowhere had inflammatory or ulcerative changes, not even in those patients who had had diarrhea. There was no evidence that the infection had originated in the mucosa and had passed through the intestinal wall to involve the peritoneum. In practically all the cases there were mild degenerative changes in the liver; in a third the spleen was enlarged and showed evidence of infection, while the kidneys were microscopically free from damage. The enlarged mesenteric glands resembled those seen in any other type of peritonitis or systemic infection.

## COMMENT

Primary or metastatic streptococcic peritonitis is defined as a peritoneal involvement which has not spread directly from a contiguous source of infection. In all except one of the cases at the Mount Sinai Hospital Str. haemolyticus (beta) was present in the peritoneal exudate which was obtained at laparotomy, at autopsy or by abdominal puncture. There are few large series reported,<sup>3</sup> and there must be many cases which are not recognized. The origin of the peritonitis is most frequently an acute infection of the upper respiratory tract. Many cases have been observed during epidemics of streptococcic sore throat,<sup>4</sup> and some cases have been observed in which the condition complicated erysipelas<sup>5</sup> or scarlet fever.<sup>6</sup>

The streptococci reached the peritoneum through the blood stream. Blood cultures are positive in 40 per cent, often within a day after peritoneal involvement. The monobacterial and general peritoneal involvement indicate this hemotogenous route, although a selective affinity of this organism for the peritoneum has not been proved.<sup>4b</sup> Visceral abscesses are rarely seen, but this might be due to the short duration of the condition in the fatal cases. However, abscesses of the skin were present in three patients who recovered.

The lymphatic system rarely plays the leading rôle in metastasis. In one instance, acute pharyngitis was followed by descending retropharyngeal, mediastinal and, ultimately, retroperitoneal phlegmon. Peritonitis was thought due to the rupture of a suppurative mesenteric lymph gland. Those who believe that the lymphatics are the only pathway of spread<sup>7</sup> also believe that the abundant lymphoid tissue at the ileocecal region and in the appendix causes the peritonitis to start

3. (a) Barrington-Ward, L. E.: Pneumococcal and Streptococcal Peritonitis, Brit. M. J. 2:704 (Oct. 15) 1932. (b) Duncan, J. H.: Primary Peritonitis, Canad. M. A. J. 24:778 (June) 1931. (c) Lipshutz, B., and Lowenburg, H.: Pneumococic and Streptococic Peritonitis, J. A. M. A. 86:99 (Jan. 9) 1926. (d) Rabinowitz, M. A.: Acute Hematogenous Streptococic Peritonitis, Am. J. M. Sc. 157:797 (June) 1919.

4. (a) Capps, J. A., and Miller, J. L.: The Chicago Epidemic of Streptococcus Sore Throat, and Its Relation to the Milk Supply, J. A. M. A. 58:1848 (June 15) 1912. (b) de la Chapelle, A.: Beitrag zur Kenntnis der sogenannten primären akuten Streptokokkenperitonitiden mit besonderer Berücksichtigung ihrer Beziehungen zur Angina tonsillaris, Arb. a. d. path. Inst. d. Univ. Helsingfors 2:583, 1907. (c) Hamburger, L. P.: An Epidemic of Septic Sore Throat in Baltimore, J. A. M. A. 58:1109 (April 13) 1912. Rabinowitz.<sup>3d</sup>

5. Pfau, C. C.: Postmortem Analysis of Etiology of Peritonitis, J. Missouri M. A. 30:72 (Feb.) 1933.

6. Kojis, F. G., and McCabe, E. J.: Primary Peritonitis Complicating Scarlet Fever, Am. J. M. Sc. 185:710, 1933.

7. Pribram, B. O.: Ueber Lymphangitis Mesenterialis, Arch. f. klin. Chir. 140:589, 1926. de la Chapelle.<sup>4b</sup>

here.<sup>3c</sup> However, this must postulate a reversal of the normal direction of the abdominal lymphatic flow. Moreover, the peritoneal symptoms rarely start or localize in the lower right quadrant but are diffuse over the abdomen. The mesenteric adenopathy is seen in the minority of cases; when present, it resembles the adenopathy seen in any general peritonitis.

The third route of infection is by the intestinal tract.<sup>8</sup> Stasis at the cecum is said to favor the passage of ingested bacteria through the parietes at this point.<sup>9</sup> Streptococci can be cultured from the peritoneum over ulcers of the mucosa.<sup>10</sup> However, they can also be cultured from the serous surfaces of the intact intestine after the ingestion of the organisms.<sup>11</sup> The fact that streptococci are sometimes cultured from the feces does not necessarily indicate this to be the mechanism of involvement. It seems that peritonitis due to this means would display the same mixed intestinal flora seen in perforations of the lower part of the bowel.<sup>12</sup> This theory postulates a selective permeability of the intestines for *Str. haemolyticus*, which has not been proved to exist. All microscopic sections show the bacteria penetrating the wall of the bowel inward from the serosa, which disproves this hypothesis.

The recoveries of the patients 6 months and 1½ years old seem to be the only instances on record of the recovery of a child less than 2 years of age, thus reducing the mortality in the twenty-five cases in this age group to 92 per cent. The previous 100 per cent mortality in children less than 2 years of age stresses the nature of the reaction of the peritoneum to infection. In infants, the peritoneum has marked absorbing powers without the ability to form localizing adhesions. While the absorptive properties persist through life, the peritoneum develops its defensive mechanism of encapsulation, which, with the growth of the omentum, determines the lowered mortality in older children and adults.

The injection and granular appearance of the serosa at the onset of infection do not differ from the picture seen in any other general peritonitis.<sup>12</sup> There is a rapid formation of the thin exudate con-

8. Fraenkel, A.: Ueber peritoneale Infektion, *Wien. klin. Wchnschr.* 2:241, 1891.

9. Barber, W. W.: Primary Streptococcic Peritonitis in Children, *Colorado M. J.* 29:324 (Aug.) 1932.

10. Wile, S. A., and Saphir, O.: Migratory Peritonitis: A Clinicopathologic Study of So-Called Hematogenous Peritonitis in Children, *Am. J. Dis. Child.* 43:610 (March) 1932.

11. Bail, M.: Die Schleimhaut des Magendarmtractes als Eingangspforte pyogener Infektionen, *Arch. f. klin. Chir.* 62:369, 1900. Mandl, F.: Beitrag zur Frage der kryptogenetischen Peritonitis, *Deutsche Ztschr. f. Chir.* 182:289, 1923. Fraenkel.<sup>8</sup>

12. Klemperer, P.: Personal communication to the author.

taining many hemolytic streptococci and pus cells. The amount of the free exudate often exceeds a liter, even in a small child. Small fibrin plaques with scant, threadlike adhesions form on the serosa. Hemolytic streptococci excrete an enzyme which dissolves human fibrin.<sup>13</sup> This explains the failure to produce firm adhesions and the fulminating course of the disease. At early operation and at autopsy, the pus is unconfined beneath the abdominal wall, with no interintestinal loculations. Since abscesses between intestinal loops are seen late in cases of peritonitis, their absence in cases of streptococcic peritonitis is probably due to the virulence of infection and the short period of survival. The infection penetrates through the intestinal serosa, so that pus cells and organisms can be found in the subserosa. Paralytic ileus with gastric retention occurs often. When encapsulation does occur, it usually starts about two weeks after the onset of the illness. Some exudates which are felt only by rectum may resolve spontaneously.

When the acutely ill child is seen, the temptation is to operate for fear that an obscured appendicitis may be present. Contrary to the opinion of others,<sup>14</sup> I believe that operation is not indicated in all cases. One must be fortified by statistics. Hematogenous streptococcic peritonitis is most common in children under 2 years of age and occurs most frequently during the winter, while appendicitis is rare in this age group, constituting less than 1 per cent of all cases of appendicitis<sup>15</sup> and occurring in children more often during the summer.<sup>15a</sup> It is in this dilemma that paracentesis is of such value.

The smear and culture of the aspirated peritoneal exudate are most important. The failure to get fluid does not necessarily exclude peritonitis. Smears showing only gram-positive cocci in short chains with an ultimate culture of *Str. haemolyticus* conclusively indicate streptococcic peritonitis and practically exclude appendicitis. No statistics are available on the bacteriologic picture of peritonitis secondary to appendicitis in infants, owing, undoubtedly, to the rarity of the disease. In childhood, however, aerobic cultures show pure *B. coli* in half the cases and *B. coli* mixed with *Staphylococcus*, *Str. viridans* or *Pneu-*

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13. Tillett, W. S.: The Occurrence of Antifibrinolytic Properties in the Blood of Patients with Acute Hemolytic Streptococcus Infections, *J. Clin. Investigation* **14**:276 (March) 1935.

14. Schwartz, J.: Primary Streptococcic Peritonitis in Children, *Surg., Gynec & Obst.* **45**:590, 1927. DeSanctis, A., and Nichols, R.: Primary Peritonitis in Children, *Arch. Pediat.* **46**:17 (Jan.) 1929. Barrington-Ward,<sup>3a</sup> Duncan,<sup>3b</sup> Lipshutz and Lowenburg.<sup>3c</sup>

15. (a) Abt, I. A.: Appendicitis in Infants, *Arch. Pediat.* **34**:641 (Sept.) 1917. (b) Freedman, H.: Appendicitis in Children, *ibid.* **46**:604, 1929. (c) Gordon, H.: Periappendicitis Without Appendicitis, *Arch. Path.* **19**:185 (Feb.) 1935. (d) Lipshutz, B.: Appendicitis in Infancy, *Arch. Pediat.* **48**:649, 1931. (e) Stone, C.: Appendicitis in Children, *Arch. Surg.* **30**:346 (Feb.) 1935.



nococcus in the remainder.<sup>16</sup> Pure growths of *Streptococcus* are found in less than 1 per cent of all cases of appendical peritonitis, and most of them are the viridans form.<sup>17</sup> *Streptococcus* is not found more abundantly because *B. coli* when present so rapidly overgrows it.<sup>18</sup> Anaerobic cultures are difficult and tedious to make, but show obligate anaerobes<sup>19</sup> and *B. Welchii* in 90 per cent of the cases.<sup>20</sup> Cultures of the emulsified walls of inflamed appendixes grow only *B. coli* and *Str. viridans*.<sup>21</sup>

Appendicitis in children between 2 and 5 years of age is distinguished from the adult type by its greater tendency to perforation and more frequent spreading peritonitis,<sup>22</sup> the mortality being 13 per cent. Pain, spasm and tenderness in the lower right quadrant occur in from 72 to 96 per cent of the patients.<sup>23</sup> The temperature averages between 101 and 103 F., and the leukocyte count in cases in which perforation occurs is between 16,000 and 20,000.

The following conditions must be considered in the differential diagnosis:

**Pneumococcic peritonitis.** The onset of pneumococcic peritonitis resembles that of the streptococcic form in the sudden, diffuse abdominal pain, distention, tenderness and vomiting. The temperature often rises to 104 F. It is more frequently seen in females and is almost exclusively a disease of childhood, particularly of the first decade. In the early stage, pneumococci may be found in the vaginal secretion. Absolute diagnosis depends on the finding of gram-positive diplococci in pure culture on abdominal puncture. Localization of the peritoneal infection is commonly seen in the later stages, so that the prognosis is better than in the streptococcic type.

**Acute serous peritonitis.** This condition, which, strictly speaking, is not peritonitis, may occur at any age. The slight general abdominal pain

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16. Farr, C. E., and Brakeley, E.: *Appendicitis in Children*, S. Clin. North America **8**:1193 (Oct.) 1928. Stone.<sup>15e</sup>

17. Farr, C. E.: *Appendicitis in Children*, Arch. Pediat. **46**:335, 1929. Zim-mer, S.: Zur Serumtherapie der Peritonitis, Arch. f. klin. Chir. **175**:727, 1933.

18. Deaver, J. B.: Remarks upon Appendicitis, Ann. Surg. **27**:303, 1898; Appendiceal Peritonitis, Surg., Gynec. & Obst. **47**:401, 1928.

19. Runeberg, B.: Studien über Bacterienformen und ihre pathogenetische Bedeutung in appendicularer Peritonitis, Arb. a. d. path. Inst. d. Univ. Helsingfors **2**:271, 1907.

20. Jennings, J. E.: Relation of the Welch Bacillus to Appendicitis and Its Complications, Ann. Surg. **93**:828, 1931.

21. Dorsey, A. H.: Bacteriology and Pathogenesis of Appendicitis, Surg., Gynec. & Obst. **50**:562, 1930.

22. (a) Baumgartner, C.: *Appendicitis in Children*, Arch. Pediat. **50**:571, 1933. (b) Churchman, J. W.: *Appendicitis in Children*, Bull. Johns Hopkins Hosp. **20**:31, 1909.

23. Freedman.<sup>15b</sup> Stone.<sup>15e</sup> Baumgartner.<sup>22a</sup>

may be more severe over McBurney's point; the soft distention, coupled with fever, the temperature rising as high as 102 F., and leukocytosis, may suggest appendicitis. The clear fluid obtained by abdominal puncture contains no organism and often no white blood cells. The needless laparotomy reveals no abdominal pathologic process except for diffuse slight injection or pink color of the peritoneum. There are varying quantities of serous, sterile fluid. The most common causes are infections of the periperitoneal tissue, such as the umbilicus and urachus,<sup>24</sup> and systemic infections, such as rheumatic fever<sup>25</sup> and grip. The proper therapy is to recognize the innocence of the peritoneal cavity and to treat the causative infection. Sometimes laparotomy is unnecessarily performed on patients with streptococcemia, who not infrequently have a sterile, serous peritoneal transudate.

Acute exudative tuberculous peritonitis. This type of peritonitis in children and adolescents may present a confusing picture. The preceding pulmonary manifestations, the protracted course of the disease, the low temperature, the milder complaints referable to the abdomen, the doughy or nodular feel of the abdomen, the tuberculin reaction, the character and bacteriologic picture of the peritoneal fluid and results of inoculation into animals are all important in diagnosis.

Mesenteric lymphadenitis. This condition is most common in persons about 13 years of age, when the mesenteric glands are at their maximum size.<sup>26</sup> The pain may be intermittent and of moderate severity. There are tenderness and inconstant rigidity over McBurney's point, and distention is often absent. The temperature rarely rises over 101 F., and the leukocyte count ranges between 12,000 to 17,000. The patient usually does not appear acutely ill, and careful examination may reveal the enlarged mesenteric glands through a thin, relaxed abdominal wall.

#### SUMMARY

Metastatic streptococcic peritonitis is a well defined entity which merits more serious consideration than has heretofore been accorded. Analysis of forty-two cases at the Mount Sinai Hospital leads to the belief that the condition can be readily recognized in most instances when one is cognizant of the characteristic clinical course and diagnostic methods.

The important features of streptococcic peritonitis are: (a) It is seen most frequently in infants; (b) it is usually preceded by pharyn-

24. Hinrichsen, H. M.: Peritonitis serosa acuta und Urachus-Entzündung, *Arch. f. klin. Chir.* **171**:627, 1932.

25. Wood, F. C., and Eliason, E. L.: Rheumatic Peritonitis. *Am. J. M. Sc.* **181**:482, 1931.

26. Mead, C. H.: Mesenteric Lymphadenitis, *Arch. Surg.* **30**:492 (March) 1935.

gitis; (c) the abdominal symptoms, early distention and constant pain and tenderness, are generalized and start from two to three days after the subsidence of the infection of the respiratory tract; (d) the condition is definitely diagnosed by abdominal puncture, the gram-positive streptococci with pus cells being pathognomic.

The treatment depends on the severity and stage of the illness, each case being a rule unto itself. The mortality, at its lowest, is 80 per cent. The frequent severe sepsis interdicts early operation, while the peritonitis is generalized. In the interim, supportive treatment is used. This consists of continuous intravenous drip of saline solution, repeated transfusion of blood and the injection of pooled antistreptococcus serums. Laparotomy is valueless and even dangerous when the sepsis is severe. However, when the general infection is not marked and there is evidence of much peritoneal fluid, improvement is often noted when drainage is obtained by the simplest and most rapid means. The large walled-off abscesses should be drained.

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## NEUROFIBROMA AND NEUROFIBROSARCOMA OF PERIPHERAL NERVES

UNASSOCIATED WITH RECKLINGHAUSEN'S DISEASE: A REPORT  
OF TWENTY-FIVE CASES

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AND

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Neoplasms of the peripheral nervous system are relatively uncommon, but their occasional occurrence and variable prognosis warrant their study with a view to standardizing, as far as possible, the methods of treatment. New growths of the cutaneous nerves and nerve trunks have long been recognized when they occur in the form of Recklinghausen's disease, and the problems relevant to this condition have been well recorded in the past and current literature. Less attention has been paid, however, to the isolated tumors of nerves when unaccompanied by generalized neurofibromatosis, and it is our purpose in this communication to record our experiences with this type of growth. The twenty-five cases herewith presented illustrate the various pathologic changes and indicate the sites at which neurofibroma and neurofibrosarcoma of the peripheral nerves are commonly encountered. While the distal portions of the cranial nerves do not strictly belong to the "peripheral nerves," we have taken the liberty of including one case in which there was a tumor of the face presumably arising from the middle branch of the fifth cranial nerve and two cases in which there were tumors arising from the vagus nerve in the neck. We have excluded consideration of the related benign tumors of the sheath of the acoustic nerve and of the spinal cord roots which have been fully treated in the monographs of Cushing<sup>1</sup> and Elsberg,<sup>2</sup> respectively. We have also excluded neoplasms of the sympathetic nervous system, which fall into a special group necessitating separate discussion.

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From the Departments of Surgery and Pathology of the Peter Bent Brigham Hospital and the Harvard Medical School.

1. Cushing, H.: *Tumors of the Nervus Acusticus*, Philadelphia, W. B. Saunders Company, 1917.

2. Elsberg, C. A.: *Tumors of the Spinal Cord*, New York, Paul B. Hoeber, Inc., 1925.

## PATHOLOGIC STRUCTURE

*Normal Nerve Sheaths.*—It is well to preface a discussion of the tumors of the nerve sheath by briefly reviewing the structures which normally comprise the neural envelops. The nerve fiber, if it is a medullated one, is surrounded by a thin layer of myelin which, supposedly, is concerned with the insulation of the nerve pathway, and encircling a myelinated or unmyelinated fiber there is a supporting coat, which is called the neurilemma or the sheath of Schwann. This sheath, which modern writers generally agree is of ectodermal origin (Masson<sup>3</sup>), is interrupted at short, rather regular intervals of a millimeter or less at the nodes of Ranvier. An aggregation of such covered fibers is encased by a perineurium which holds the group together as a bundle. A number of these fasciculi are in turn surrounded by the epineurium to constitute the nerve proper. Peripheral nerve fibers, as well as the fibers of their integuments, have a finely wavy character as contrasted to those of the brain and spinal cord, and theoretically this waviness protects the nerve from injury by allowing it to stretch during movements of a limb or viscus.

*Neurofibroma.*—From the sheath of Schwann there arises a benign tumor known as a neurofibroma, schwannoma, neurilemoma or perineural fibroblastoma. The terms perineural fibroblastoma (Mallory,<sup>4</sup> Penfield<sup>5</sup>) and neurilemoma (Stout<sup>6</sup>) have been proposed in order to separate this tumor from that form which occurs in Recklinghausen's disease. In this communication, however, we continue to apply the term neurofibroma to all of the benign tumors of the nerve sheaths, whether or not they are associated with Recklinghausen's disease, but we realize that some authors employ it only for the generalized type. Whether the isolated growth takes origin from the neurilemma, perineurium or epineurium is difficult to determine, but probably all three may give rise to the neoplasm under consideration. There have been heated discussions concerning which of the nerve investments is responsible for the development of such a growth, but we do not find the arguments on either side entirely convincing, and hence we do not wish to enter into the vexed problem of ectodermal or mesodermal origin of this

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3. Masson, P.: Experimental and Spontaneous Schwannomas (Peripheral Gliomas), *Am. J. Path.* 8:367, 1932.

4. Mallory, F. B.: The Type Cell of the So-Called Dural Endothelioma, *J. M. Research* 4:349, 1920.

5. Penfield, W.: The Encapsulated Tumors of the Nervous System, *Surg., Gynec. & Obst.* 45:178, 1927; Tumors of the Sheaths of the Nervous System, in *Cytology and Cellular Pathology of the Nervous System*, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 955.

6. Stout, A. P.: The Peripheral Manifestations of the Specific Nerve Sheath Tumor (Neurilemoma), *Am. J. Cancer* 24:751, 1935.

tumor. In any event, its essential character is that of a connective tissue growth, differing from the ordinary fibroma of other organs in several respects, as presently described. Slow growth characterizes this neoplasm, and the gradually expanding fusiform or rounded mass becomes well demarcated from the surrounding soft tissues. As enlargement proceeds, the nerve is not incorporated into the tumor but is pushed to one side or is expanded. The latter characteristic is often important if one desires to remove a neurofibroma and yet maintain the continuity and function of the nerve trunk. Grossly, such a neoplasm is encapsulated and may be peeled away from the nerve which courses along one edge or surface. The external surface is gray or yellowish gray. Degeneration is common, and cystic change may be so extensive that the mass consists of little more than a shell, filled with clear or slightly cloudy, watery or mucinous fluid and traversed by a few remaining threads or bands of tissue (fig. 21 B). This transition may be so extensive as to obscure the original character of the growth. Degenerative changes appear to be more common in the tumors which arise in the neck but are also seen in those originating from nerves of the extremities.

The microscopic picture identifies a neurofibroma and is the same as that presented by the well known acoustic neurinoma. The connective tissue fibrils of the neurofibroma occur as long, wavy strands which coalesce into bundles of varying size and form interlacing bands and whorls (figs. 22 and 32). The cells may deposit little or no intercellular substance but usually elaborate collagen in considerable quantities. Collagenous bundles may be hyalinized. The nuclei are narrow, elongated, pointed, hyperchromatic and of a mature type. Mitotic figures are rarely seen. Of particular significance is the arrangement of the cell nuclei in parallel rows, "like nuclei on parade," each being closely packed against neighboring ones. Not all neurofibromas present this feature as strikingly as is illustrated in figure 19, but some degree of this configuration is usually encountered. Blood vessels are not numerous but may be rather large, often appearing as blood sinusoids. Axis-cylinders are found only where the mass is attached to the nerve trunk or where nerve fibers are carried passively into the peripheral portions of the tumor. Degenerative change is common, and this finding often helps one to make the diagnosis. Loss of cell structure, accumulation of interstitial fluid and myxomatous changes appear, and hence there may be a variation from a high cellularity to a loose-textured growth (fig. 3). Commonly, there are foamy phagocytic cells, either scattered in small groups (fig. 29) or accumulated in larger numbers in areas of cystic degeneration. Stains for fat, such as scarlet red, show the lipid character of the debris contained in these cells.

*Malignant Neurofibroma.*—In the following series of cases we encountered three specimens which had a somewhat more rapid rate

of growth than that of the ordinary neurofibroma, and yet the degree of malignancy was not sufficient to warrant a diagnosis of neurofibrosarcoma. The histologic picture was rather similar to that presented by benign neurofibroma, but several features evinced a more rapidly growing tumor (fig. 24). The cytoplasm of the cells was more abundant, and the individual fibrils were not as long. The nuclei were shorter and more plump, had less chromatin and were more vesicular in appearance. Occasional nucleoli and rare mitotic figures were encountered. We have hesitated to designate these as sarcomas, for metastases did not occur. There was, however, a strong tendency to local recurrence and even to massive regional extension if they were not completely excised. The term malignant neurofibroma is a poor one, but we have employed it in three cases to indicate a rapidity of growth which is between that of the neurofibroma and that of the neurofibrosarcoma. Such a tumor was seen in case 22, and while there were no metastases such as might be expected from invasion of blood vessels, still there was extensive slow growth over a period of thirteen years, which eventually led to death. In case 19 it was impossible to remove one of these neoplasms surgically, and we have reason to believe that it may ultimately prove fatal to the patient. In case 18 this rather rapid type of growth was again encountered, but in this instance there was clean removal of the mass and the adjacent nerve trunk, and we entertain the belief that this patient will have no recurrence.

*Neurofibrosarcoma (Neurogenic Sarcoma).*—This tumor, which has previously been studied by Quick and Cutler,<sup>7</sup> Stewart and Copeland<sup>8</sup> and Stout,<sup>9</sup> also arises from the connective tissue coverings of the nerve fibers and fasciculi. It may arise secondarily in a previously existing benign neurofibroma, as is illustrated by case 4. More often, however, rapid growth is evident from the first appearance of the mass (cases 7 and 10). When the tumor is exposed at operation, its malignant nature may be evident by the absence of a capsule, by its infiltrative properties and by the presence of regional extensions of metastases. Not infrequently, however, a well defined capsule is observed, and regional tissue may show no evidence of invasion. In this case the operator is led to believe that he is dealing with a benign lesion. This is particularly prone to occur when there is secondary degeneration in the central part of a previously existing neurofibroma. Hence the clinical history of

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7. Quick, D., and Cutler, Max: *Neurogenic Sarcoma*, *Ann. Surg.* **86**:810, 1927.

8. Stewart, F. W., and Copeland, M. M.: *Neurogenic Sarcoma*, *Am. J. Cancer* **15**:1235, 1931.

9. Stout, A. P.: *The Malignant Tumors of the Peripheral Nerves*, *Am. J. Cancer* **25**:1, 1935.

recent active enlargement may be more important to the surgeon than the gross findings at the operating table.

These sarcomas present a variable picture. If they have arisen in previously existing benign tumors, some areas will show evidence of slow growth, such as capsule formation, but other portions are more indicative of malignancy. There may be adhesions to surrounding muscle or other soft tissue, and externally the grayish or grayish red surface is irregular, roughened and hemorrhagic. The cut surface is granular, soft and often friable. Areas of hemorrhage are common.

Microscopically, evidence of rapid growth is shown by the high cellularity, the variation in size of cells, the formation of giant cells and the presence of mitotic figures (figs. 10 and 15). The individual cells are of younger type, possess abundant but poorly outlined cytoplasm, have shorter cell processes and stain irregularly. If some areas of less rapid growth are present, there will be changes similar to those presented by a neurofibroma, such as the formation of bands of elongated wavy cells in bundles and whorls with some palisading of nuclei. One is often not fortunate enough to find the latter changes, and histologically it may be impossible to do more than make a diagnosis of fibrosarcoma, relying for the final diagnosis of nerve tumor on the gross picture of origin from a nerve trunk.

(*Recklinghausen's Disease*.—For purposes of comparison, the histologic picture in generalized neurofibromatosis must be briefly mentioned. The widespread nodular involvement of the cutaneous and larger nerves, the laxity of the skin and the cutaneous pigmentation are well known. A high hereditary factor and a tendency to malignant degeneration are often encountered. The condition may widely affect the extremities, body, neck or head but is occasionally confined to one region, such as the face or trunk. Coincidentally, there may be involvement of thoracic or abdominal viscera, sympathetic nerves or meninges. The swellings of the nerve trunk are rounded or fusiform and quite irregular in size or shape. The condition is probably something more than a neoplasm in the usual connotation of the term, and possibly represents some congenital or inherited tendency to malformation of the nerve. Histologically, there is a distinct difference from the ordinary neurofibroma, for intermixed with the connective tissue overgrowth in generalized neurofibromatosis there is a diffuse and rich supply of nerve fibers of either medullated or nonmedullated types.)

#### DISTRIBUTION OF TUMORS

The statement has occasionally been made that these tumors may arise from nerves in any part of the body, but a closer analysis of cases shows that they are found commonly in certain areas, that in others they are rare and that in several places they have never been reported.



Stout<sup>6</sup> has made a study of benign tumors of the nerve sheaths (neurilemoma), including his own cases and those reported in the literature. Figure 1, a composite chart, shows the distribution of tumors in Stout's cases and the distribution of the reported cervical neurofibromas of Mayo and Barber,<sup>10</sup> and also of our twenty benign lesions. The tendency of these growths to appear in selected regions makes it advisable to discuss the various sites separately.

*Extremities.*—Since the longest courses of peripheral nerves lie in the extremities, it is not surprising that these neoplasms are most numerous in the arms and legs. In the arms they may occur along any portion of the major nerve trunks but appear to be somewhat more com-

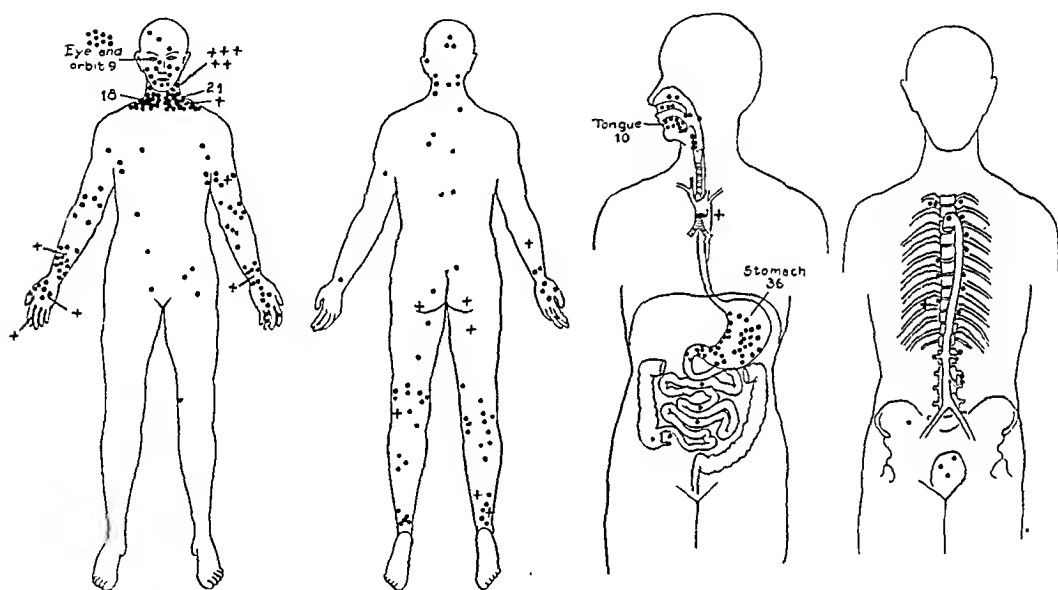


Fig. 1.—Distribution of benign tumors of the sheaths of peripheral nerves. (After Stout.) In addition to the tumors in the cases reported and collected by Stout, the cervical neurofibromas of Mayo and Barber are charted. Our twenty personally observed benign neurofibromas are indicated by crosses.

mon on the median or ulnar nerves at or just above the wrist. They may be found also along the smaller nerve branches of the hands and fingers. Since the major nerves course along the flexor surfaces of the arms and legs, it is not surprising that most of these growths occur on the anterior aspect of the arms and the posterior portions of the legs. The sciatic nerve gives rise to some of the growths in the lower extremity, but the popliteal space and the malleolar regions are common sites. The larger growths occur on the sciatic nerve in the middle third or the upper

10. Mayo, C. W., and Barber, K. W.: *Cervical Neurofibroma*, Surg., Gynec. & Obst. 59:671, 1934.

third of the thigh, but smaller ones are often found along the branches of the tibial or the peroneal nerves. The feet rarely give rise to these neoplasms, but we have seen two such examples which are not included in the present series. Peers<sup>11</sup> has recorded a case in which a neurogenic sarcoma arose within the shaft of the ulna.

*Neck.*—The neck, with its multiplicity of cranial nerves, sympathetic nerves and branches of the brachial plexus, is one of the favorite regions for the development of tumors of the nerve sheaths, and in the presence of a mass in the neck of an adult the possibility of a neurofibroma must be strongly considered. Of the various regional trunks, the cervical sympathetic or a spinal nerve root is probably the most frequently involved, but the vagus, the spinal accessory and hypoglossal nerve (Friedman and Eisenberg<sup>12</sup>) have all been found to be attached to such a growth. Not infrequently, however, it is impossible to tell at the operating table the exact origin of the mass, for the depth of the wound or the obscured position on the under-side of the tumor makes identification of the nerve difficult. In two of our patients we were unable to ascertain the nerve involved, and in a third case we could do little more than infer that the mass was attached to one of the anterior roots of the cervical plexus. Mayo and Barber<sup>10</sup> recorded seventeen examples of cervical neurofibroma, exclusive of those arising in the brachial plexus, and our series includes five such cases. The brachial plexus is responsible for two additional neoplasms in our patients, one arising from the posterior cord and the other from the lateral cord.

*Face.*—Neurofibroma may be encountered occasionally on the face, the branches of the fifth nerve being most commonly affected. While such a growth may involve only the extracranial tissues, there are a few examples of extension upward through the foramen ovale or rotundum into the cranial vault, or the site of origin may be just at one of the cranial foramina and growth proceed both intracranially and extracranially. This results in a so-called "dumb-bell" tumor, the narrow area representing that part lying in the bony canal. In case 19 a cystic, malignant neurofibroma apparently arose from the second division of the trigeminal nerve, for there was an external bulge low in the temporal fossa, with extension into the orbit and also downward through the pterygopalatine fossa into the soft palate.

*Mouth, Pharynx and Larynx.*—Ten neurofibromas have been reported in the tongue and sublingual regions, occurring in all parts of the tongue

11. Peers, J. H.: Primary Intramedullary Neurogenic Sarcoma of the Ulna, *Am. J. Path.* **10**:811, 1934.

12. Friedman, L., and Eisenberg, A. A.: Neurofibroma of the Hypoglossal Nerve, *Ann. Surg.* **101**:834, 1935.

from its tip to the base. Several specimens have been removed from the hard palate. Rare examples of isolated neurofibroma have been reported in the pharynx. In Figi's<sup>13</sup> case 1 the mass projected into the posterolateral wall of the pharynx and displaced the tonsil inward toward the midline. The mass, when removed, was 3 cm. in diameter. The nerve from which it arose was not known for certainty, the patient exhibiting no disability after the surgical removal. Three cases have been recorded in which the tumor occurred in the aryepiglottic folds of the larynx (Vail<sup>14</sup>).

*Thorax.*—The intercostal or phrenic nerves may give rise to a neurofibroma in the thorax, which often attains a considerable size. The benignity of the tumor makes surgical removal a most satisfying procedure, and one who is familiar with operations on the thoracic wall and in the cavities of the chest has little difficulty in completely enucleating such a growth. In one instance (case 20) a neurofibroma 6 cm. in diameter lay between the left parietal pleura and the great vessels of the heart. Keller and Callender<sup>15</sup> recorded a somewhat similar case, but with the tumor lower down, between the pericardium and the left lung. An example of neurofibroma of an intercostal nerve is seen in case 21, in which instance the mass was 12 cm. in diameter, was well encapsulated and was attached to the eighth intercostal nerve, from which it bulged into the pleural cavity. The relative softness of the lungs or other intrathoracic structures often allows one of these neoplasms to expand readily and assume a great size. Harrington<sup>16</sup> reported fourteen cases of mediastinal or intrathoracic perineural fibroblastoma, and his success in treating these lesions again emphasizes the desirability of recognizing such benign growths and attempting surgical extirpation. Of forty-six various intrathoracic tumors removed at operation, this author classified fourteen of them as of nerve sheath origin, and ten of these occurred in the posterior mediastinum. (The presence of a neurofibroma in the posterior mediastinum and in the neck may lead to a dumb-bell-shaped tumor which passes through into the spinal canal. The subject of the so-called hour-glass tumors of the spine has been fully treated by Heuer<sup>17</sup>).

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13. Figi, F. A.: Solitary Neurofibroma of the Pharynx, *Arch. Otolaryng.* **17**: 386 (March) 1933.

14. Vail, H. H.: Schwannoma of the Larynx, *Ann. Otol., Rhin. & Laryng.* **42**: 476, 1933.

15. Keller, W. L., and Callender, G. R.: Neurofibroma Arising on the Pericardial Pleura, *Ann. Surg.* **92**:666, 1930.

16. Harrington, S. W.: Surgical Treatment in Fourteen Cases of Mediastinal or Intrathoracic Perineural Fibroblastoma, *J. Thoracic Surg.* **3**:590, 1934.

17. Heuer, G. J.: The So-Called Hour Glass Tumors of the Spine, *Arch. Surg.* **18**:935 (April) 1929.

*Abdominal Cavity.*—The abdominal cavity occasionally contains a neoplasm of the sort under discussion; our series, however, does not include an example of this. The recorded cases reveal the stomach as the most commonly involved viscus and Stout has accepted the growths in thirty-five cases as being truly tumors of the nerve sheaths. Case <sup>18</sup> described a neurofibroma, 6 cm. in diameter, on the posterior wall of the stomach. In the Cabot <sup>19</sup> case 18283, one of these benign growths, 12 cm. in diameter, projected inward from the posterior wall of the stomach. Three or four have been found in the small intestine and one in the cecum, but no case has been reported of such a tumor in the colon or the rectum which was considered authentic. There are isolated reports of these growths appearing along the retroperitoneal tissues.

*Skin.*—For the purpose of completeness, mention is made of the small nonencapsulated neurofibroma of the skin. Lesions of this type have relatively little importance but must be included in a discussion of tumors of the nerve sheaths. They are small, varying from 5 to 6 mm. to somewhat more than 1 cm. in diameter and from 3 to 5 mm. in thickness. They arise in the corium, do not possess a well developed capsule and are usually removed with the diagnosis of fibroma of the skin. The histologic features, however, are similar to those of the larger tumors of the nerve sheaths seen elsewhere. These small cutaneous lesions have appeared in multiple locations on the surface of the body, often on the back, chest or abdomen, frequently on the extremities and rarely in the neck, but not, in our experience, on the head. We have encountered ten of these cutaneous lesions, but include only two for purposes of illustration.

#### AGE AND SEX DISTRIBUTION

The benign or malignant tumors of the nerve sheaths are largely encountered in early or middle adult life. They have been found in childhood but are more often seen in the third, fourth or fifth decades. Approximately two thirds of our patients were between the ages of 20 and 50 years, this distribution roughly corresponding to that found in the literature.

In regard to the occurrence of the benign and malignant tumors in males and females, there is no greater tendency for them to occur more commonly in either sex. Thirteen of our patients were men, and twelve were women.

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18. Case, J. T.: Three Cases of Neurqma: Cirroid Neuroma of Face, Neurofibroma of Stomach, Posterior Nerve Neurofibroma, *Am. J. Surg.* 8:648, 1930.

19. Unusual Cause of Hematemesis (Neurofibroma of Stomach), Cabot Case 18283, *New England J. Med.* 207:91, 1932.

## SYMPTOMS AND SIGNS

The frequency with which these tumors are incorrectly diagnosed preoperatively indicates that few characteristic findings are exhibited by them. There are, however, several general symptoms or signs which are associated with these growths as they occur in various locations on the body. The most common complaint is that of a local swelling, and with the slowly growing neurofibroma this may be present over a period of many years and show only slight progression during that time. Tumors of ten or fifteen years' duration or even longer are not infrequent. Contrary to this, a short duration, of from several months to a year, and rapid augmentation in size are the rule in a neurofibrosarcoma. The overall dimensions of the growth have no prognostic value regarding its benignity or malignancy. The size of the local mass may vary greatly, as can be gleaned by reference to the tabulated list of cases. The smallest lesions were little more than pea-sized swellings along the nerve, while the largest were from 12 to 14 cm. in diameter. The large proportion of these were firm and hard, but the tendency to cystic degeneration must be remembered, and when this occurs transillumination may be demonstrated. In case 16, even when well exposed at operation, the cystic structure was thought to be probably a branchial cleft cyst, and it was not until microscopic examination of the few remaining trabeculae within the cyst that the correct diagnosis was established. The direction of the mobility of the mass may give a clue concerning the attachment to a nerve, for it can be easily moved from side to side, but it is harder to displace it longitudinally along the course of the nerve. Of course, if the growth is a malignant one, it may be well bound down to the surrounding structures. The sarcoma does not metastasize by lymphatics but rather tends to invade blood vessels; hence the absence of involvement of the regional lymph node does not rule out a diagnosis of a malignant growth. In cases in which the presence of sarcoma is suspected, early roentgenograms of the lung may be of assistance in reaching a proper diagnosis and in withholding useless surgical intervention, since pulmonary metastases occur early.

When situated in the mediastinum or the thoracic cage, the local mass often reaches such proportions as to interfere with the surrounding vital structures and thus give rise to symptoms relating to partial obstruction of the venae cavae, the respiratory passages or the esophagus. With a tumor of the hour-glass variety, the outstanding symptoms may be referable to pressure on the spinal cord. In the pharynx or larynx, obstruction of the respiratory tract or difficulty in phonation are the usual symptoms. In the stomach there is little to distinguish such a growth from other benign ones. In this location the tumor is often so small as to be of little importance, but it may reach such proportions

that it is palpable through the abdominal wall. If the growth projects into the stomach it may obstruct the lumen or ulcerate and produce severe hemorrhage.

The incidence of pain is variable, so much so that it cannot be greatly relied on for diagnostic importance. Pain may be of two sorts. First, it may be present in the mass itself, though this is by no means a constant feature. Secondly, the pain may be referred along the nerve to which the tumor is attached. When this radiation is encountered, it may be continuous or may be elicited only when pressure is applied externally on the tumor or when the limb or part is placed in such a position that the neoplasm is compressed by the neighboring tissues. Thus, in case 18 there was pain referred to the forearm and hand when the arm was so moved that the clavicle impinged against a tumor of the brachial plexus. This patient could also elicit the referred pain in the hand by making digital pressure in the supraclavicular fossa. It is well to emphasize again, however, that pain may be absent.

Contrary to what one might expect, paresthesia, hypesthesia, anesthesia or motor paralysis is not commonly encountered along the distribution of the nerve involved by a benign growth. This is due to the fact that the nerve trunk is usually pushed to one side or is so expanded against the soft, surrounding tissues that there is little or no disturbance in the function of the nerve. In contrast to this, malignant neural tumors are more prone to produce sensory or motor disturbances, for they tend to infiltrate the nerve proper and to destroy its fibers by local pressure. In short, then, persistent motor or sensory disturbance favors diagnosis of a malignant, rather than of a benign, lesion.

#### TREATMENT

The treatment of these growths is surgical, and radiation therapy has little place except possibly as a palliative measure in the terminal stages of neurofibrosarcoma. Local irradiation therapy, either by radium or by roentgen rays, has been almost universally disappointing.

In the surgical treatment of the neurofibroma, two methods of excision are available. By one, the tumor may be shelled out or peeled away from the nerve, leaving the shredded but functionally intact nerve unsevered. By the alternative method, the entire structure is excised, the nerve being transected on either side of the mass, and the divided nerve is then repaired by end to end suture. There are several factors which influence the choice between these two methods. First, the type of nerve involved is of considerable importance. A small branch, particularly if it is only sensory, may be divided with impunity, whereas one hesitates to divide a large trunk, such as the sciatic nerve, if it can be avoided. Secondly, the involvement of a mixed nerve tends to militate against its division by the surgeon, for restoration of function may

not be as complete as is the case when a purely sensory or purely motor nerve is divided and sutured. Finally, the obviously benign growth may be shelled out from its nerve without hesitation, but if there is any question as to undue rate of growth (such as a malignant neurofibroma) the patient should be given the benefit of the doubt, and the mass and adjacent nerve trunks should be completely and cleanly excised. The latter consideration should be stressed, for while older teachings emphasized the preservation of the nerve, we have come to believe that more radical removal of a portion of the adjacent nerve trunk may be the only method of preventing recurrence. Indeed, we are convinced that in case 18, one of a tumor of the brachial plexus, this course has been well justified. Certainly, this malignant neurofibroma could not have been cleanly removed from the ensheathing nerve, and local recurrence would have occurred. Suspecting the possible rapid growth, we removed the entire mass and nerve trunk. There has been complete restoration of function in the arm, and in three years there has been no evidence of recurrence. We <sup>20</sup> have discussed these operative considerations more fully in a separate publication.

The preceding paragraph deals with the local removal of tumors having a slow or moderate rate of growth. In the highly malignant forms, however, early amputation of the extremity may be a life-saving measure, if performed before metastases have occurred. One should act exactly as one does when dealing with periosteal sarcoma of bone. Amputation should be proposed only when the roentgenogram does not reveal pulmonary metastases, and finally the removal of an arm or leg must be justified by establishing the diagnosis of malignancy on pathologic examination. Such study can be rapidly performed by frozen section preparations and amputation decided on and executed immediately if the findings demand it. We feel reasonably certain that amputation at the first operation in case 4 would have given a chance for complete removal of all of the sarcomatous tissue in this patient.

#### REPORT OF CASES <sup>21</sup>

The following series of twenty-five personally observed cases includes twenty examples of benign neurofibroma occurring in various parts of the body, as follows: arm, five; leg, five; neck, six; mediastinum and thoracic cage, two, and skin, two. Several of the lesions from the neck showed marked cystic degeneration, and one from the peroneal nerve was also largely cystic. Malignant neurofibroma was encountered three times, once in the subcapsular region, once on the

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20. Cutler, E. C., and Gross, R. E.: *The Surgical Treatment of Tumors of the Peripheral Nerves*, *Ann. Surg.* **104**:436 (Sept.) 1936.

21. Dr. Harvey Cushing, Dr. John Homans and Dr. David Cheever gave us permission to include case 8, case 16 and cases 5, 17 and 20.

face and once in the brachial plexus. Neurofibrosarcoma was seen twice on the sciatic nerve and once on the median nerve. The tumor on the median nerve developed in a previously existing benign neurofibroma which had been present for twenty years, but the two sarcomas of the leg showed evidence of rapid growth from their first appearances.

Surgical extirpation was attempted in all of our cases, with but two exceptions. In case 10, one of an extensive sarcoma of the thigh, only partial removal was done in an effort to relieve the local discomfort. In case 19 the deeply rooted growth in the temporal and pterygopalatine fossae defied surgical removal; only small fragments could be resected, and the remaining cystic portion was swabbed out with a sclerosing fluid.<sup>22</sup> In the remaining twenty-three cases local excision was performed in each instance, the usual procedure being to shell the mass away from its nerve trunk. In only two instances were major nerve trunks completely divided during operative procedure. In case 13 the left vagus was severed (and not sutured), with resulting permanent hoarseness. In case 18 the completely divided posterior cord of the brachial plexus was resutured, and the resulting loss of function of the radial and axillary nerves has subsequently been fully restored by regeneration of the nerve.

In none of our cases of benign neurofibroma has there been evidence of recurrence, the patients being followed over periods ranging from several months to nineteen years. Of the three patients with malignant neurofibroma, one died of the disease thirteen years after operation, one had a local recurrence within six months and one has been followed three years without recurrence, the last patient being the only one of the three who underwent complete extirpation at operation. Of the three patients with neurofibrosarcoma, all died within one year with extensive pulmonary metastases. The various cases are summarized in the table, and brief case reports are appended.

CASE 1.—A. C., a 30 year old woman, was first seen on Feb. 6, 1932, complaining of a localized, oval, nonpainful swelling on the flexor surface of the left wrist, which had gradually increased in size over a period of two years. Examination showed a firm, elongated, nontender mass, 5 cm. long and 1.5 cm. in diameter, toward the lateral aspect of the volar surface of the wrist. There was slight hypesthesia at the tip of the index finger.

*Operation.*—A hard nodular tumor was exposed, which lay on and was attached to the median nerve (fig. 2). This mass was removed and was dissected away from the nerve trunk, injuring only a few of the nerve fibers.

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22. A modification of Carnoy's fluid, after Zollinger and Moritz (Effects of Necrobiotic Agents on the Walls of Cysts Experimentally Produced in the Brains of Dogs, Arch. Neurol. & Psychiat. 28:1046 [Nov.] 1932). The composition is absolute alcohol, 6 cc.; chloroform, 3 cc.; glacial acetic acid, 1 cc., and ferric chloride, 1 Gm.



*Data in Twenty-Five Cases of Neuroplasm of the Peripheral Nervous System \**

Case	Sex Age	Type of Tumor	Size and Weight of Tumor	Nerve Involved and Location	Preoperative Duration, Years	Result
Arms						
1	F 30	Neurofibroma	4.5 x 1.7 x 1.3 cm.	Median, wrist	2	Not followed
2	M 81	Neurofibroma	2 x 1.5 x 1 cm.	Ulna, wrist	7	Not followed
3	F 65	Neurofibroma	3 x 2.5 x 1.5 cm.	Median, cutaneous, palm (?)	10	No recurrence in 12 years
4	M 56	Neurofibrosarcoma	18.5 x 15 x 13 cm.	Median, upper part of arm	20; recent rapid growth	Died in 1 year; metastases
5	F 70	Neurofibroma	2 x 1.5 x 1 cm.	Digital, finger	..	.....
6	M 22	Neurofibroma	4.5 cm. long; 1.8 cm. in diameter	Posterior branch of ulna, forearm	1	No recurrence in 12 years
Legs						
7	F 32	Neurofibrosarcoma	10 x 9 x 6 cm.	Sciatic	1	Died in 1 year; metastases
8	M 42	Neurofibroma	5 cm. long, 1.5 cm. in diameter	Common peroneal, knee	3½	No recurrence in 19 years
9	M 48	Neurofibroma	15.5 x 7 x 5 cm.	Superficial peroneal, ankle	10	No recurrence in 5 years
10	M 74	Neurofibrosarcoma	18 x 12 x 10 cm. 827 Gm.	Sciatic	3½	Died in 1 year; metastases
11	F 40	Neurofibroma	1 x 0.9 x 0.6 cm.	Posterior tibial, ankle	3	.....
6	M 22	Neurofibroma	8 x 5.5 x 5.5 cm. 122 Gm.	Sciatic	5	No recurrence in 12 years
Neck						
12	M 19	Neurofibroma	4.5 cm. in diameter	?	3	Not followed
13	M 74	Neurofibroma	6 x 4 x 3 cm. 32 Gm.	Left vagus	5	No recurrence in 5 years; hoarseness produced by section of vagus nerve
14	M 38	Neurofibroma	10.5 x 7 x 6 cm. 253 Gm.	Vagus	15	No recurrence in 5 years
15	F 70	Neurofibroma	8 x 5 x 4.5 cm. 75 Gm.	?	10	No recurrence in 3½ years
16	F 66	Neurofibroma	6 x 3.5 x 2.5 cm.	Anterior root of a cervical nerve (?)	3	No recurrence in 6 months
Brachial Plexus						
17	F 36	Neurofibroma	2.5 cm. in diameter	Lateral cord	8	Not followed
18	M 23	Malignant neurofibroma	4.7 cm. long; 2.4 cm. in diameter	Posterior cord	1	No recurrence in 3 years
Face						
19	F 32	Malignant neurofibroma	4.5 cm. in diameter (?)	Maxillary branch of trigeminal (?)	7	Recurrence in 6 months (?)
Mediastinum and Thoracic Wall						
20	M 35	Neurofibroma	6 x 5.5 x 4 cm.	? Left phrenic, mediastinum	10	No recurrence in 17 years
21	F 27	Neurofibroma	8.8 x 7.6 x 7.8 cm. 326 Gm.	8th intercostal, right	5	No recurrence in 3 years
Back and Perineum						
22	F 30	Malignant neurofibroma	7 x 2.5 x 2 cm.	Long subscapular, beneath scapula (?)	1½	Recurrence in 6 months; regional and thoracic extensions until death 14 years later
23	F 41	Neurofibroma	Five nodules; largest, 3 x 1.5 x 0.8 cm.	Perineal nerve, perineum	7	No recurrence in 13 years
Skin						
24	M 32	Neurofibroma	1.5 cm. in diameter; 1.2 cm. thick	Cutaneous nerve, thigh	6	.....
25	M 33	Neurofibroma	5 mm. in diameter	Cutaneous nerve, arm	..	.....

\* Surgical removal was employed in each case.

*Result.*—After operation there were slight tingling and numbness on the flexor aspect of the tip of the index finger as well as along the lateral border of this finger. The patient was followed for only one month after operation.

*Pathologic Examination.*—The firm, white, nodular and encapsulated structure measured 4.5 cm. in length, 1.7 cm. in width and 1.3 cm. in thickness. The cut surfaces presented faint, white, linear markings or streaks against a faintly grayish white background.

The microscopic picture was typical of that presented by a neurofibroma, with a loose-textured growth of low cellularity. The cells were long, and wavy and of mature type and had formed an abundant collagen. Moderate palisading of nuclei was present.

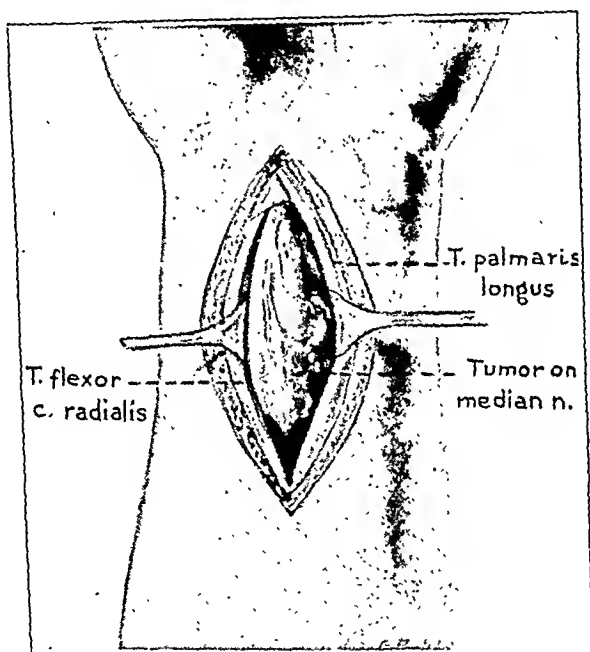


Fig. 2 (case 1).—A lobulated neurofibroma arising from the median nerve. At operation the mass was dissected away from the nerve, leaving the trunk intact.

**CASE 2.**—H. M., an 81 year old man, entered the hospital on Oct. 8, 1920, for treatment of a small mass on the right wrist, which had been present for seven years. Pain in the wrist was a prominent symptom, and there was radiation of this pain down into the palm of the hand. There was a rather firm, tender mass on the ulnar side of the flexor aspect of the right wrist. This seemed to be deep in the tissues, and while freely movable it was apparently adherent to some of the underlying structures.

*Operation.*—On operation the mass was found to be incorporated in the substance of the ulnar nerve sheath, most of the fibers of which could be seen running along the posterior wall of the tumor. These were carefully dissected away, and finally the whole tumor shelled out easily, leaving the nerve essentially intact.

*Result.*—Complete relief from pain was obtained. After operation there was slight diminution in sensation over the ulnar distribution of the little finger and the

ring finger. Abduction and adduction of the fingers were accomplished slowly and with difficulty. The patient was lost track of one month after operation.

*Pathologic Examination.*—The tumor consisted of a smooth, firm, glistening, encapsulated growth measuring 2 by 1.5 by 1 cm. The cut surface was moist and gray.

Microscopic examination showed a typical neurofibroma. Long wavy cells appeared, with interlacing bundles and whorl formations. Many nuclei showed definite palisading. Many areas had a loose-textured myxomatous structure of low cellularity, but these were intermingled with zones of more cellular, compact tissue (fig. 3). In a few portions of the tumor there were occasional large mononuclear phagocytes, laden with lipoid material.

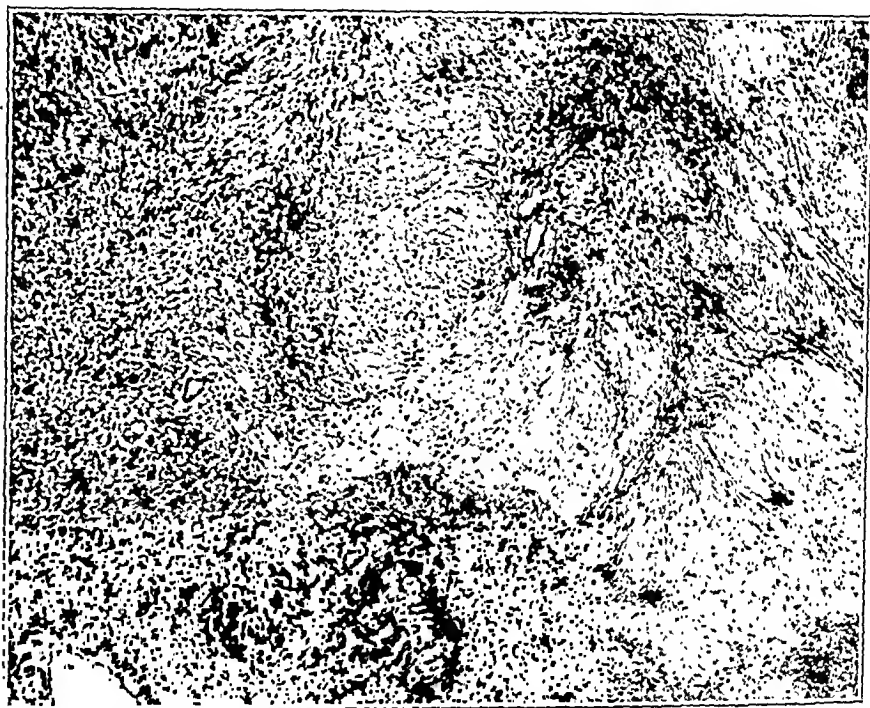


Fig. 3 (case 2).—Low power photomicrograph ( $\times 60$ ) of a benign neurofibroma (from the wrist), showing the great variability in cellularity. Note the more compact tissue toward the left and the loose-textured, reticular substance in the center and toward the right.

CASE 3.—M. B., a 65 year old woman, was seen on Jan. 15, 1923, complaining of a lump on her hand which had been present for ten years. This had gradually grown larger, but had given no symptoms except for the inconvenience caused by having it on the palm. Examination showed a subcutaneous palmar mass, which was nontender and about the size of an English walnut.

*Operation.*—The mass was easily removed, being apparently attached only to the palmar fascia. (It probably arose from one of the cutaneous twigs of the median nerve.)

*Result.*—The patient has been followed until 1935, during which time there has been no recurrence.

*Pathologic Examination.*—The specimen consisted of a small pinkish gray, well encapsulated tumor, measuring 3 by 2.5 by 1.5 cm. which, on section, had a variegated appearance. Some areas were grayish white and glistening, while others were deep red and soft, and contained considerable blood clot.

Microscopic examination showed, intimately attached to the dense palmar fascia, a typical neurofibroma, many areas of which were undergoing cystic degeneration. The better preserved, wavy fibrillary connective tissue had an abundant intercellular substance. The long spindle cells were arranged in bundles, which ran in various interlacing fasciculi, and the nuclei appeared in palisade arrangements. No mitoses were found.

CASE 4.—F. H., a 56 year old man, entered the hospital on May 27, 1931, for treatment of a nonpainful swelling of the upper part of the right arm which had been present for about twenty years. The slowly growing mass had produced little inconvenience for many years, but during the past five months it had more than doubled its size. Examination showed a large, rounded, firm swelling on the anteromedial aspect of the upper part of the arm, coursing over which were many greatly dilated veins (fig. 4 A). The mass was warm and had the appearance of a

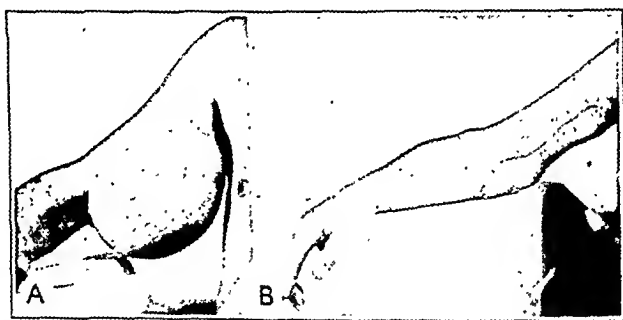


Fig. 4 (case 4).—A, a photograph (May 28, 1931) of a tumor of the median nerve which had been present for twenty years and had doubled its size in the past five months. B, a photograph after local removal of the tumor.

rapidly growing tumor, yet it was smooth and apparently within a capsule. There were no axillary or pulmonary metastases. Muscles of the fingers and wrist seemed weak, but there were no areas of anesthesia.

*Operation.*—On operation the upper end of the lesion was seen to spring from the median nerve, which thinned out over the capsule of the tumor. The mass was dissected away from the median nerve, but portions of the brachial artery and veins had to be removed because they were surrounded by tumor. Circulation in the right arm was adequately maintained by collateral vessels. There was no postoperative change in the motor or sensory functions of the right arm. Figure 4 B shows the condition of the arm ten days after operation.

*Pathologic Examination.*—The largely encapsulated tumor weighed 2,200 Gm. and had an ovoid, fairly uniform contour, measuring 18.5 by 15 by 13 cm. (fig. 5). The cut surface was mottled yellowish pink and was crossed by interlacing strands and broad bundles of white and yellowish tissue. In the center and about the periphery of one pole there were irregular zones of gelatinous softening and hemorrhage (fig. 6).

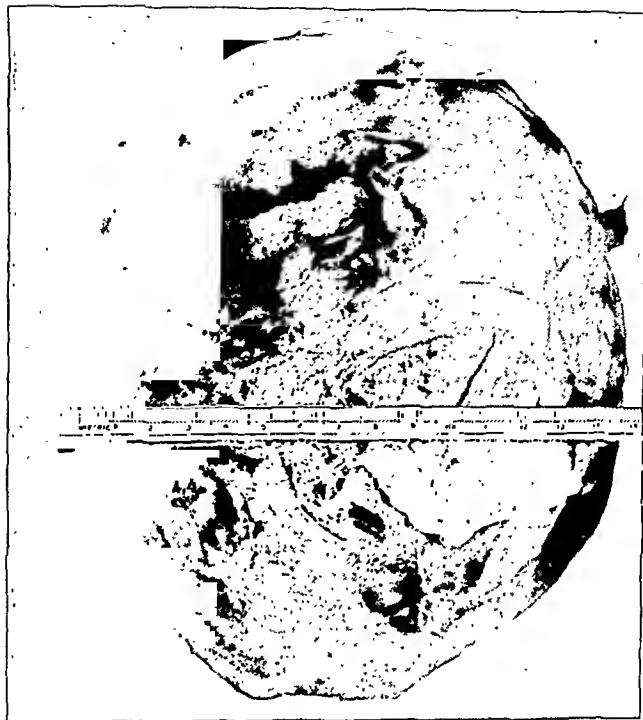


Fig. 5 (case 4).—External view of the tumor of the median nerve.

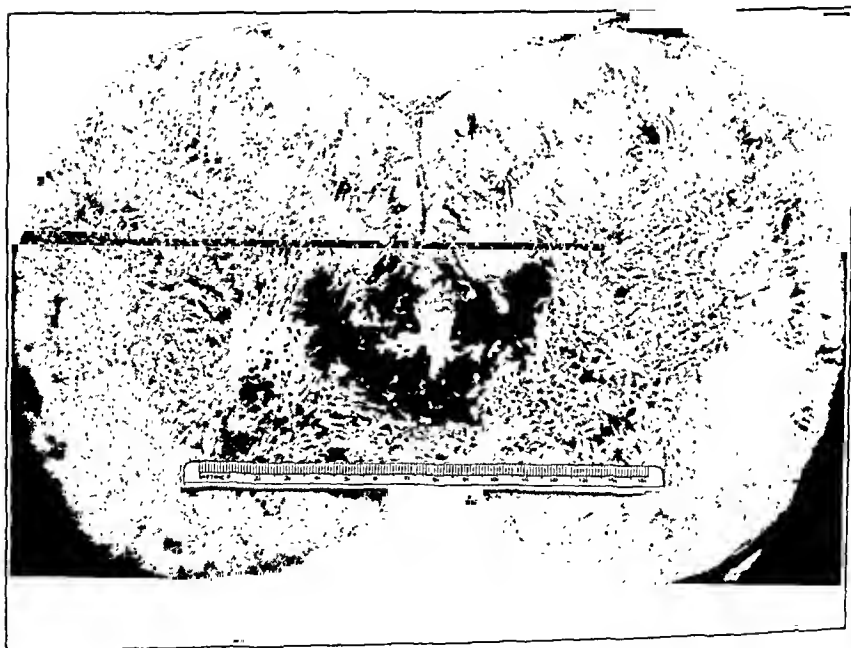


Fig. 6 (case 4).—Cut surface of the tumor of the median nerve. (From *Ann. Surg.* 104:436 [Sept.] 1936.)

Microscopic examination showed rather higher cellularity than is usually seen in a neurofibroma. The general picture was one of elongated cells with mature hyperchromatic, long nuclei, the cells occurring in long interlacing and whorled fasciculi. Palisading of nuclei was seen in many places. In some zones the tumor had a loose-textured appearance, and there was evidence of cellular and cystic degeneration. There were some features which would mark this as a malignant type of growth, but these were overlooked at the time. In many regions, particularly where the cellularity was high, the nuclei were broader, more rounded and more immature in appearance, presenting considerable variation in size, shape and staining qualities. The cell processes in these zones were also shorter than those seen in the more slowly growing areas. No mitotic figures were encountered, and the diagnosis of neurofibroma was made. It is unfortunate that additional material is not available for a check-up examination, for it is almost certain that additional blocks from other portions of the growth would establish the presence of malignancy.

*Second Entry* (Oct. 31).—During the four months since previous discharge from the hospital, a recurrent mass had developed over the entire upper part of the right arm (fig. 7), and there was marked edema below the elbow. There was also a nodule in the left pulmonary field, visible by roentgen examination, which was believed to represent a metastatic tumor. As the arm was useless and was certainly going to cause great distress, amputation was performed in spite of the presence of pulmonary metastases.

*Result.*—Roentgenograms of the chest in April 1932 showed extensive involvement of the lungs by metastatic tumor, and the upper half of the left lung field was completely obliterated (fig. 8). Seven intensive treatments with high voltage roentgen rays were given over the chest, with little relief. The patient died in May 1932. Permission for autopsy was not obtained. We are convinced that this patient should have had more radical treatment at the first operation. An incision into the mass at the operating table would have excluded hemorrhage or cystic degeneration as the cause of its great increase in size. Amputation should then have been performed immediately.

*Second Pathologic Examination.*—Over the anterior and medial lower two thirds of the humerus lay a large, irregular tumor, consisting of four quite well separated portions (fig. 9). The median nerve could be traced through the upper portion of the tumor down to this site of former operation, where the nerve frayed out and was lost. The portions of neoplasm measured 11 by 11 by 10 cm., 11 by 9 by 10 cm., 7 by 6 by 3 cm., and 11 by 8 by 3 cm., respectively. The median nerve emerged from the inferior aspect of the large distal tumor and proceeded on the normal course into the forearm. All of the masses appeared to be fairly well encapsulated, and no direct extension into adjacent structures could be demonstrated. On cut section the various nodules were very friable and grayish pink. As a whole they were quite soft and of homogeneous structure, except for the central portions, which were rather necrotic.

The microscopic picture was that of a highly cellular, very malignant, rapidly growing fibrosarcoma (fig. 10). While there was some interlacing of bundles and whorl formation, it would be difficult to say that this was a tumor of the nerve sheath had it not been previously known that it arose in a neurofibroma and was attached to the nerve trunk. The nuclei were all large and vesicular in appearance and had a finely divided and well dispersed chromatin material. The nuclei varied considerably in size and particularly in staining reaction. One or two nucleoli were often seen. Mitotic figures were extremely numerous, and multipolar

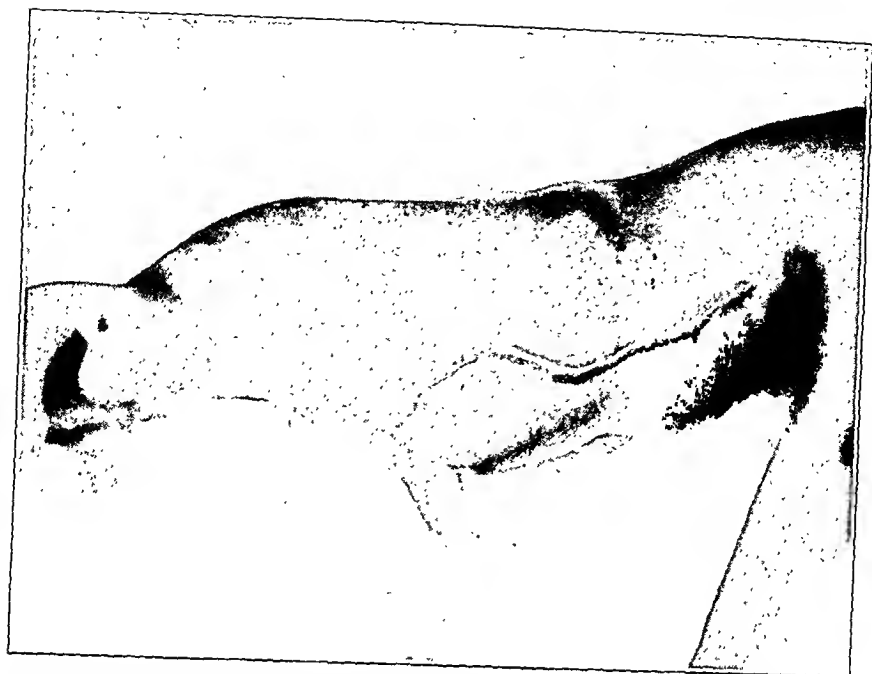


Fig. 7 (case 4).—Recurrent neurofibrosarcoma of the median nerve, photographed four and one-half months after figure 4 B.



Fig. 8 (case 4).—Roentgenogram of the chest (April 1932) showing extensive pulmonary metastases from the neurofibrosarcoma of the median nerve.



Fig. 9 (case 4).—The recurrent neurofibrosarcoma of the median nerve after removal. The size of the tumor mass can be compared to the humeral shaft seen in the right lower portion of the photograph.

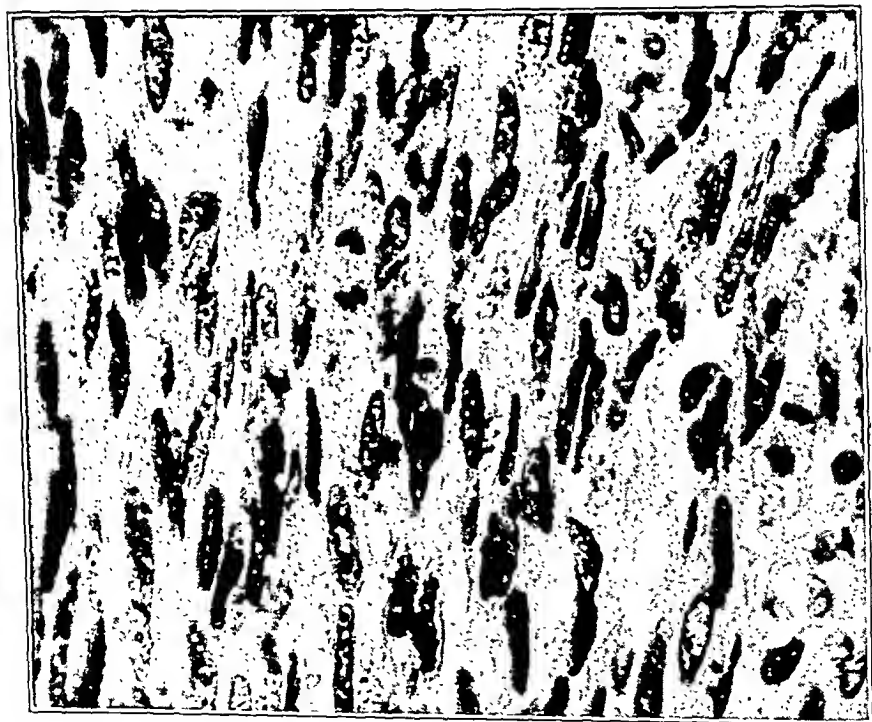


Fig. 10 (case 4).—Photomicrograph ( $\times 700$ ) of the recurrent neurofibrosarcoma shown in figure 9. The nuclei vary in size, shape, staining reaction and chromatin content. There are cytoplasmic outlines and short fibrillary processes. Two mitotic figures are shown in the field.



mitoses were occasionally encountered. Cytoplasm of the cells were abundant, but the cell processes were not very long and laid down only a minimal amount of intercellular collagen.

CASE 5.—M. S., a 70 year old woman, seen in January 1927, had had a slowly growing mass on the palmar aspect of the right forefinger for ten years. The presence of the mass caused considerable interference with manual work. Examination showed a hard, rounded, nontender swelling on the volar aspect of the distal phalanx.

*Operation.*—The mass shelled out easily, no attachments to nerves being seen.

*Result.*—The patient was not followed.

*Pathologic Examination.*—The encapsulated pearly gray mass measured 2 by 1.5 by 1 cm. Cross-sections showed no degenerative changes.

The microscopic picture was typical for a neurofibroma. It was of low cellularity, with abundant intercellular collagen and little evidence of degeneration.

CASE 6.—B. G., a 22 year old man, entered the hospital on Nov. 8, 1915, because of a painful tumor in the left buttock and a painful swelling of the forearm. For five years there had been pain and tenderness in the left hip, and for four years there had been occasional, increasingly severe pain radiating down the back of the leg. For seven months there had been a large lump in the left buttock. For one year he had also had a slowly growing and painful mass on the back of the left forearm. Examination showed a hard, rounded, tender, deeply attached swelling in the lower part of the left buttock (fig. 11), and the left gluteal fold was lower than the right. The left leg was slightly smaller than the right. Motions of the hip were somewhat limited because of pain. On the back of the left forearm, halfway between the elbow and the wrist, was a tender, deep swelling. The left hypothernar eminence was somewhat smaller than the right. Extension of the fingers was not quite complete at the first interphalangeal and metacarpophalangeal joints. The patient had none of the stigmas of Recklinghausen's disease. This case had unusual interest because of the presence of neurofibromas in two siblings, unassociated with Recklinghausen's disease (the patient in case 7 and one brother not treated by us). These three cases have been previously recorded by Fleming and Marvin.<sup>23</sup>

*Operation.*—Operation on the left thigh disclosed an encapsulated growth about the size and shape of a lemon which lay directly in the middle of the sciatic nerve, the fibers of which were spiraled around the growth. The nerve was split for a distance of 8 cm., and the tumor was easily shelled out in toto. The mass removed from the dorsal aspect of the left forearm arose from the posterior branch of the ulnar nerve, from which it was peeled away without severing the nerve.

*Result.*—There was complete relief from pain, without loss of sensory or motor function, in the arm and leg. There was no recurrence of either growth when the patient was last seen in 1927.

*Pathologic Examination.*—The tumor of the arm consisted of a firm, gray, semitranslucent, oblong, smooth, somewhat nodular but well encapsulated mass, measuring 4.5 cm. in length and 1.8 cm. in diameter (fig. 12 A). The cut surface was smooth, moist and myxomatous.

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23. Fleming, L. N., and Marvin, F. W.: Familial Fibromyxomata of the Peripheral Nerves, Surg., Gynec. & Obst. 24:287, 1917.

Microscopically, there was a relatively low cellularity to the tumor, the wavy connective tissue cells laying down abundant collagen and also showing a myxomatous type of growth. No mitotic figures were seen. Interlacing bands of fibers, with a suggestion of palisading of the nuclei, gave a characteristic picture of neurofibroma.

The tumor of the leg was oblong, smoothly encapsulated, slightly irregular and lemon shaped and weighed 122 Gm. (fig. 12 *B*). It was firm, gray and slightly elastic. The cut surface was smooth, myxomatous and practically colorless. A few areas of the cut surface had the appearance of faint, interlacing bundles of connective tissue.

Microscopically, there were interlacing strands of wavy connective tissue in a loose-textured type of growth which had the general appearance of a neuro-



Fig. 11 (case 6).—Photograph of the patient to show swelling of the left buttock produced by a neurofibroma of the sciatic nerve.

fibroma. The nuclei and cytoplasm were elongated. Many of these cells were laying down considerable amounts of collagen. Edema and degenerative changes were marked. The mass had a well developed fibrous capsule.

CASE 7.—A. S. (sister of B. G., case 6), a 32 year old woman, entered the hospital on Nov. 3, 1915, with the complaint of pain in the lumbar portion of her back, radiating down to the posterior part of the right leg, and weakness of her right leg for one year. (Fifteen years previously she had had a "fibroid tumor" the size of a small orange removed from the right side of her neck in another hospital.) She dated her present illness from a fall eighteen months prior to entry, at which time she sat down heavily and received a severe jar. On subsequent development of pain in the back and legs, she had been placed in a plaster jacket for spinal immobilization. Two months prior to the time when we first saw her she had been operated on elsewhere (for tumor of the spinal cord [?]),

and a dorsal laminectomy had been performed with negative results and with no relief from symptoms. Examination showed limitation of flexion of the right hip and foot because of pain which the movements excited. In the right subgluteal fold an indistinct deep mass was palpable. There were areas of anesthesia over the dorsal surface of the toes of the right foot, extending up a distance of 2 or 3 cm. onto the dorsum of the foot and also spreading over a strip on the lateral aspect of the foot as far as the ankle. There was also a questionable



Fig. 12 (case 6).—*A*, a neurofibroma removed from the dorsal aspect of the forearm. The specimen measured 4.5 cm. in length and 1.8 cm. in its maximum diameter. *B*, a neurofibroma removed from the left sciatic nerve. (See *A*.) The specimen was lemon sized, weighing 122 Gm.

area of anesthesia over the posterior aspect of the right calf along the distribution of the first and the second sacral nerve.

*Operation.*—The sciatic nerve was exposed and was found to contain a large bulbous swelling surrounded and enclosed by the fibers of the nerve. An incision was made through the nerve capsule, and it was somewhat difficult to tell just

which was the proper layer for enucleation. It was finally possible, however, to tilt the tumor up from below by blunt dissection and to follow it into the sciatic notch. In the final stages of delivery the mass was broken into in its upper pole, and undoubtedly some fragments were left in the operative field. The thin nerve capsule was now allowed to collapse, the procedure invoking but little damage to the nerve trunk.

*Result.*—Complete relief from pain was obtained, but there were residual areas of anesthesia on the sole of the foot and also surrounding the internal malleolus. Four months later there was return of pain in the foot, and there was an obvious recurrence of an infiltrating tumor deep in the buttocks. The patient died within a year of pulmonary metastases while at another hospital. Permission for autopsy was not obtained.

*Pathologic Examination.*—The pear-shaped, slightly yellowish, but rather translucent tumor measured 10 by 9 by 6 cm. A cross-section showed three large cystic cavities filled with vesiculated tissue. The remaining mass was opaque, white, myxomatous and necrotic.

Microscopically, the neoplasm was a very cellular, highly malignant fibrosarcoma. The closely packed nuclei were oblong, loose textured young forms. There was no palisading of nuclei. There was only slight formation of intercellular substance. Mitotic figures were numerous. Areas of degeneration and necrosis were extensive.

CASE 8.—P. T. C., a 42 year old man, was seen on April 25, 1916, complaining of a swelling on the lateral aspect of the left knee, a toe drop and pain in the knee and ankle for nine months. Examination showed a hard, tender swelling, about 2 cm. in circumference, superficial to and just below the head of the left fibula. Touching this mass caused a prickling sensation in the great toe and the second toe. There was inability to dorsiflex the great toe, and an area of hypesthesia was found over the great and the second toe which extended up for a distance of 3 cm. onto the dorsum of the foot.

*Operation.*—Operation disclosed a swelling in the peroneal nerve, the nerve trunk above and below this bulbous enlargement being entirely normal. The outer fibers of the nerve were split longitudinally, bringing into view a cyst 3 cm. in length, around which the central bundles of the peroneal nerve coursed (fig. 13). It was then possible to enucleate the cyst in its entirety, cutting across only a few nerve fibers at either end of the cyst. The split nerve was allowed to collapse and was dropped back into the wound.

*Result.*—After the operation limitation of motion of the foot and toe and the areas of anesthesia were practically the same as before operation. In about one year all sensory loss had been regained, and the muscular control of the left great toe and the left foot had returned to normal. The patient has been followed until 1935 and has had no recurrence of the mass on the lateral aspect of the knee.

*Pathologic Examination.*—The mass proved to be a cystic structure about 3 cm. in length and 1.5 cm. in diameter. There was a thin, grayish capsule, which was filled with a yellowish gelatinous substance but no solid tumor tissue.

Microscopically, the wall of the cyst was composed of a thin, fibrous structure in which the individual cells were elongated and very narrow and had slightly wavy cell nuclei and cell fibrillae. These spindly cells had a slight tendency to occur in interlacing bands, but there was no evidence of palisading of nuclei. There was a small amount of intercellular collagenous substance. There were no mitotic figures. There was obvious cystic degeneration in this thin bit of

remaining tissue, and the central gelatinous substance was mucoid in appearance and took a deep basophilic stain. Along the outer aspect of the fibrous capsule there were a few medullated nerve fibers. Knowing the tendency of a neurofibroma to break down and become cystic and having the small bits of tissue histologically remaining in the wall of this cyst which are consistent with neurofibroma, we are forced to the conclusion that this myxomatous cyst of the peroneal nerve had its origin in a previously existing neurofibroma.

CASE 9.—T. M., a 48 year old man, was seen in December 1923 for treatment of a slowly growing, nonpainful mass over the right ankle, which he had had "all his life." Examination showed an elastic, tense, bilobed, partially fluctuant and partly solid tumor 15.5 cm. long, 7 cm. wide and 5 cm. in thickness over the right external malleolus.

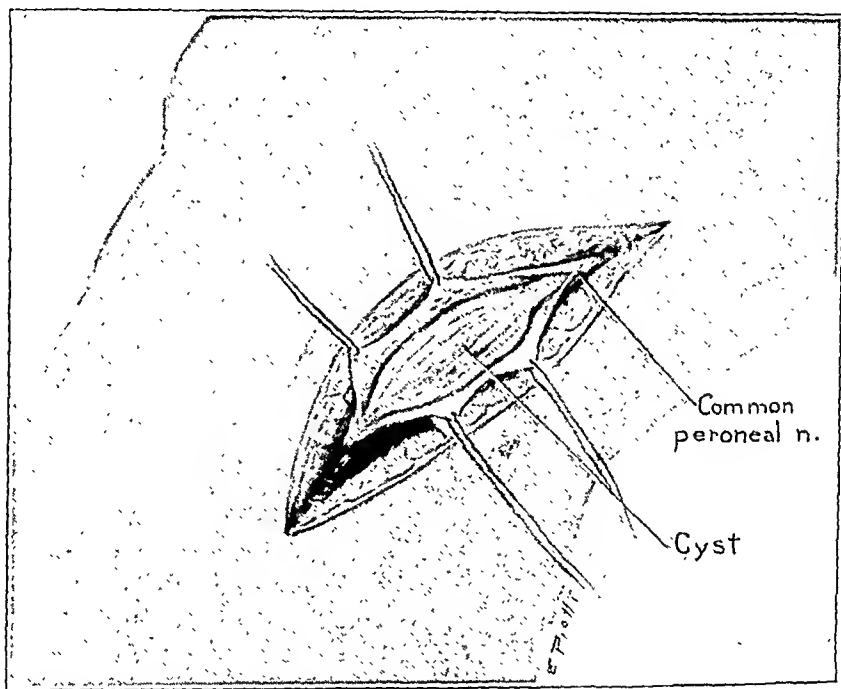


Fig. 13 (case 8).—A cyst in the substance of the common peroneal nerve, originating in a degenerated neurofibroma. The outer portion of the nerve has been incised longitudinally, and the cut edges are retracted with silk threads. The cyst lying in the central portion of the nerve trunk is surrounded by some nerve fibers from the central part of the trunk. Only these central fibers (seen at either end of the cyst) were divided in removing the cyst.

*Operation.*—On operation the tumor was found to extend deeply between the tendons. It was closely adherent to the periosteum of the fibula and was attached to the superficial peroneal nerve, from which it was peeled away.

*Result.*—There had been no recurrence up to 1932, at which time the patient was lost from observation.

*Pathologic Examination.*—The ovoid tumor measured 15.5 by 7 by 5 cm. The major portion of the well encapsulated mass was necrotic and cystic, and incision

allowed the escape of 200 cc. of thin, rather bright red bloody liquid. The cavity was one with ragged recesses and irregular projections of gelatinous yellowish tissue, having about the consistency of fibrinous exudate. About one third of the cyst was lined by translucent, yellowish gelatinous material, alternating with a dark red firmer substance. Incision of various portions of the tumor revealed calcified material in the capsule.

Microscopically, the better preserved portions of the tumor showed irregular interlacing small bundles of elongated cells in arrangements typical of a neurofibroma. No mitotic figures were seen. The nuclei varied a little more in size and shape than is usually seen in the average neurofibroma. The long cytoplasmic processes were laying down a fairly abundant intercellular collagenous material. The tumor varied considerably in cellularity from place to place. There were marked degenerative changes.



Fig. 14 (case 10).—Photograph of a large fibrosarcoma (which arose from the sciatic nerve and infiltrated the overlying hamstring muscles).

CASE 10.—E. P., a 74 year old man, entered the hospital on May 23, 1934, because of a swelling in the right thigh and pain in the right leg for nine months. Examination showed a large, firm, rather elongated, slightly tender mass about the size of a large grapefruit in the upper third of the posterior aspect of the right thigh. Roentgen examination showed a soft tissue swelling in the thigh and definite destruction of the tuberosity of the right ischium indicating invasion by tumor.

*Operation.*—On operation the large mass was found to be intimately adherent to the overlying muscle bundles (fig. 14). It was impossible to uncover the sciatic nerve at the upper end of the wound, though it was exposed at the lower pole of the tumor as it emerged from the tumor mass. The tumor was split, and the major strands of the sciatic nerve were pulled aside. The neoplasm was then

shelled out and was separated as well as possible from the surrounding soft muscular tissues. Complete extirpation of this obviously malignant tumor was impossible, and since the patient had refused amputation an attempt was made to remove only the greatest bulk of the growth in order to relieve the local discomfort.

*Result.*—Local and regional roentgen irradiation was given in four courses of treatment during the following seven months, at the end of which time pulmonary metastases were evident in roentgenograms. The patient died one year after operation, obviously with extensive pulmonary metastases. Permission for autopsy was not obtained.

*Pathologic Examination.*—The partially encapsulated, irregular and torn tumor weighed 827 Gm. and measured 18 by 12 by 10 cm. One side showed large amounts of myxomatous material, which were intermingled with zones of white,

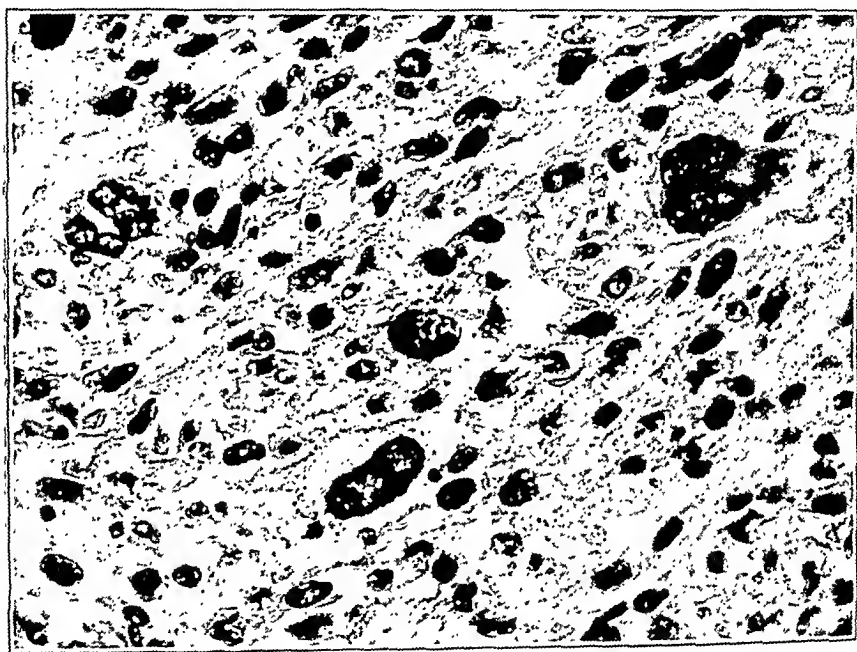


Fig. 15 (case 10).—Photomicrograph ( $\times 370$ ) of a rapidly growing fibrosarcoma originating from the sheath of the sciatic nerve. The nuclei present great variation in size. Multinucleated cells are common. (Other fields contained many mitoses.)

firm, fibrous substance. At the lower end of the tumor some fragments of the nerve trunk were seen to blend with the tumor and become inseparable from it. Cut section showed a yellowish gray appearance, varying from myxomatous material to soft and necrotic or to firm and better preserved tissue.

The histologic picture was that of a rapidly growing sarcoma, the microscopic as well as the gross structure being characterized by great variability. The highly cellular growth showed a great range in size, shape and staining properties of nuclei (fig. 15). Multinucleated cells were common, and mitoses were numerous. Collagen was seen in small amounts, and extensive areas of necrosis and hemorrhage were common.

CASE 11.—L. A., a 40 year old woman, was seen on Sept. 6, 1935, complaining of a small area of tenderness just below the right internal malleolus for three years. Examination disclosed a distinct swelling about 1 cm. in diameter.

*Operation.*—The well encapsulated mass was easily peeled away from the posterior tibial nerve.

*Result.*—There were no areas of anesthesia or motor disturbance in the foot after operation.

*Pathologic Examination.*—The firm, pinkish gray, encapsulated nodule measured 1 by 0.9 by 0.6 cm. The cut surface was firm and gray, but scattered through it were small brownish areas.

The histologic picture was one of a typical, slowly growing neurofibroma, showing small zones of early necrosis and deposition of blood pigment.

CASE 12.—F. H., a 19 year old youth, was seen on March 16, 1917, complaining of a nontender but gradually increasing swelling in the left side of the neck of three years' duration. Posterior to the upper insertion of the sternocleidomastoid muscle was a rounded, immovable, firm mass 6 cm. in diameter. Roentgen examination of the neck showed an area of rarefaction in the left side of the bodies of the fourth and fifth cervical vertebrae, suggesting pressure atrophy.

*Operation.*—An encapsulated mass was found to be in contact posteriorly with the erector spinae and longus colli groups of muscles and above lay along the lower surface of the skull. This was gradually freed by blunt dissection. The tumor appeared to have no pedicle or point of attachment. It was not known from which nerve the mass arose.

*Result.*—The patient was not followed.

*Pathologic Examination.*—The mass was smoothly rounded and well encapsulated and measured 4.5 cm. in diameter. The central part of the tumor was necrotic, gelatinous and translucent and had intermingled areas of hemorrhage. The peripheral portions of the tumor showed some solid white fibrous tissue from 2 to 5 mm. in thickness where the neoplasm was better preserved.

Microscopically, all of the sections showed typical neurofibroma and the histologic details of this type of growth. There were, however, widespread edema, evidence of degeneration with loss of histologic structure, infiltration with large phagocytes and the formation of cystic spaces ranging from 1 to 3 mm. or more in diameter.

CASE 13.—P. H., a 69 year old man, was seen on Nov. 19, 1919, with a chief complaint of cervical discomfort and a gradually increasing swelling of the left side of the neck for four months. Associated with this there had been moderate pain radiating up the left side of the neck and the region of the mastoid. During this time there had been slight hoarseness. Examination showed a pulsating, nontender swelling 2 cm. in diameter just above the bifurcation of the carotid artery. The left pupil was smaller than the right, but both reacted to light and in accommodation.

*Operation.*—On operation the lower portion of the internal carotid artery was found to be greatly twisted and looped on itself, but no other mass was discovered during cervical exploration. (Very likely there was a small mass deep to this convoluted vessel which was missed during the operative exposure.)

*Second Entry.*—The patient was not seen again until 1924, when he returned to the hospital because of progressive enlargement of the cervical mass. During the six year period there had been only moderate discomfort until five months



before entry, when the swelling became distinctly painful, with radiation from the angle of the jaw to the region of the left mastoid and occipital area as well as to the temporal region and the lateral aspect of the left eye. There was a mild unproductive cough. On the left side of the neck, slightly below the angle of the jaw, there was a firm, nontender, irregular mass 4 by 5 cm. in length and breadth. The left pupil was of pinpoint size and reacted sluggishly to light.

*Operation* (Jan. 11, 1924).—Operation revealed a rounded tumor beneath the sternocleidomastoid muscle, which had its origin high in the neck. The common carotid artery had been pushed inward and anteriorly. The mass was excised, being freed from the base of the skull where it was attached to a nerve which was obviously the vagus. This nerve was completely severed, no nerve suture being possible because of the gap produced in the nerve trunk.

*Result*.—The voice remained permanently husky (loss of function of the recurrent laryngeal nerve). There was complete relief from pain. There had been

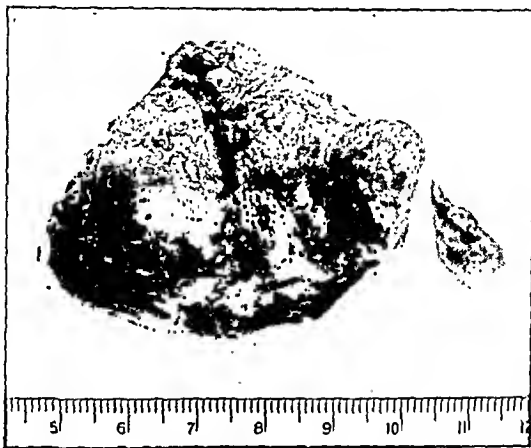


Fig. 16 (case 13).—Neurofibroma removed from cervical portion of the vagus nerve.

no recurrence of pain or of the mass up until 1929, when the patient died of pneumonia. (This case has particular interest from the consideration of complete division of the left vagus nerve, for during the five years of life after division of this nerve we were unable to detect any change in the cardiac mechanism or variation in function of the abdominal viscera.)

*Pathologic Examination*.—The oval, irregular, lobulated, gray and pinkish, encapsulated mass measured 6 by 4 by 3 cm. and weighed 32 Gm. (fig. 16). Some areas were firm and others were somewhat soft. The cut surface was homogeneous, but in the opaque white substance were small hemorrhagic areas.

Microscopically, there was a low cellularity, an interlacing of bundles of spindle-shaped cells, with long, delicate cytoplasmic extensions and some deposition of intercellular collagen. The cells had oval, slightly granular nuclei with scanty cytoplasm, the nuclei being frequently arranged in definite palisades, and in some areas this finding was striking. No mitotic figures were encountered. A few scattered areas showed some evidence of early degeneration.

CASE 14.—C. H., a 38 year old man, was first seen on Sept. 26, 1930, because of swelling on the left side of the neck which had been progressively increasing in size for fifteen years. Operation on this mass had been performed at another hospital one year previously, and a large cyst was entered which was said to be "the size of a grapefruit." It was firmly adherent to the surrounding structures, and attempts at excision were not made. Examination now revealed a conspicuous ovoid, rather smooth, semifluctuant mass, approximately the size of two fists, which extended from the angle of the jaw down nearly to the clavicle. It could be moved quite freely from side to side but not up and down. Involvement of the recurrent laryngeal nerve was suggested by the presence of hoarseness.

*Operation.*—The tumor was outlined posteriorly, inferiorly and medially. The carotid artery was finally exposed as it lay on the medial aspect of the tumor,

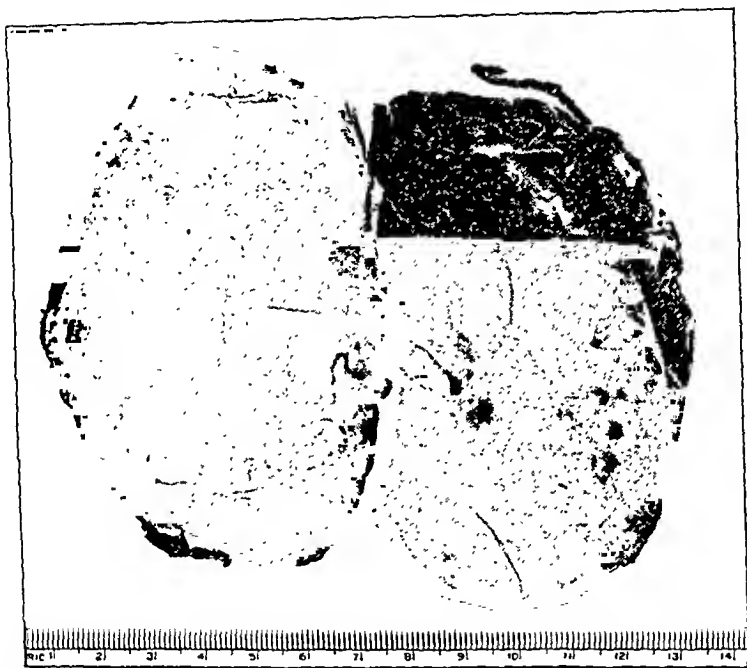


Fig. 17 (case 14).—Cut surface of a large cervical neurofibroma arising from the vagus nerve.

together with a large nerve, which was proved to be the vagus. Without great difficulty a complete enucleation of this tumor was effected (without severing the nerve). Posteriorly, the mass lay against the transverse processes of the cervical vertebrae, passing upward nearly to the base of the skull.

*Result.*—The patient has been followed until April 1935, with complete relief from symptoms and without evidence of recurrence.

*Pathologic Examination.*—The tumor was roughly elliptical, smooth and well encapsulated; it weighed 253 Gm., and measured 10.5 by 7 by 6 cm. The cut surface presented a solid, glistening, yellowish gray tissue, with small punctate areas showing necrosis (fig. 17).

Microscopically, the better preserved areas showed anastomosing bands of elongated and narrow, fusiform cells, with long wavy fibrillae, showing charac-

teristic structures of a neurofibroma. There was some palisading of nuclei. There was evidence of extensive degeneration as shown by edema of the tumor and presence of numerous vacuolated foam cells.

CASE 15.—A. C., a 70 year old woman, was seen on Sept. 11, 1931, complaining of a mass on the left side of her neck which had gradually increased in size over a period of ten years. At the angle of the jaw was a firm, nontender,



Fig. 18 (case 15).—*A*, external surfaces of a well encapsulated cervical neurofibroma. *B*, cut surfaces of a cervical neurofibroma, showing extensive central degeneration and cyst formation.

slightly movable, questionably cystic swelling about the size of a lemon, extending from the lobe of the left ear to about 4 cm. above the clavicle.

*Operation.*—On operation a large tightly stretched nerve was found coursing transversely across the upper portion of the tumor. There was a similar nerve

trunk stretched transversely across the lower pole of the mass. It was impossible to identify with certainty these nerve structures. It was certain, however, that they were not the spinal accessory nerves or portions of the ansa hypoglossi nerves. These were dissected upward and downward, and the tumor was then freed from the surrounding tissue without breaking its capsule.

*Result.*—The patient was last seen in January 1935, at which time there was no evidence of recurrence.

*Pathologic Examination.*—The well encapsulated, ovoid tumor measured 8 by 5 by 4.5 cm. and weighed 75 Gm. (fig. 18A). Cut section showed a cystic and necrotic center with better preserved tumor tissue at the periphery (fig. 18B).



Fig. 19 (case 15).—Photomicrograph ( $\times 170$ ) of a benign neurofibroma with typical palisading of nuclei.

Microscopically, the cells were elongated and spindle shaped, but wavy, with long fibrillar structures, between which there was an abundance of intercellular collagen. Nuclei were elongated and slightly wavy. There was a marked tendency to palisading of nuclei (fig. 19). In many areas there was evidence of degeneration and cyst formation. The picture was typical of a degenerating neurofibroma.

CASE 16.—L. B., a 66 year old woman, entered the hospital on Feb. 1, 1935, complaining of a mass on the left side of the neck which had been present for three years. While growth had been slow at first, the mass had rapidly increased in size during the last year. There was a marked swelling of the left side of the neck, extending from the angle of the jaw down to a point about opposite the level of the hyoid bone. Palpation revealed a firm, freely movable, somewhat cystic-feeling mass, which was nontender. At first, it seemed as if it

pushed the carotid vessels forward, a pulsation being prominent on the anterior aspect of the mass. The swelling was about 7 cm. in length, the long axis being in the vertical plane of the body, and about 3.5 cm. in width. There was edema of the left tonsil and a marked bulge in the left tonsillar fossa.

*Operation.*—Operation disclosed the tumor partly overlain by the internal jugular vein and its branches, and it was necessary to tie these off and resect them from the lower part of the tumor. The external carotid artery had been pushed forward by the mass, and the internal carotid artery was greatly displaced

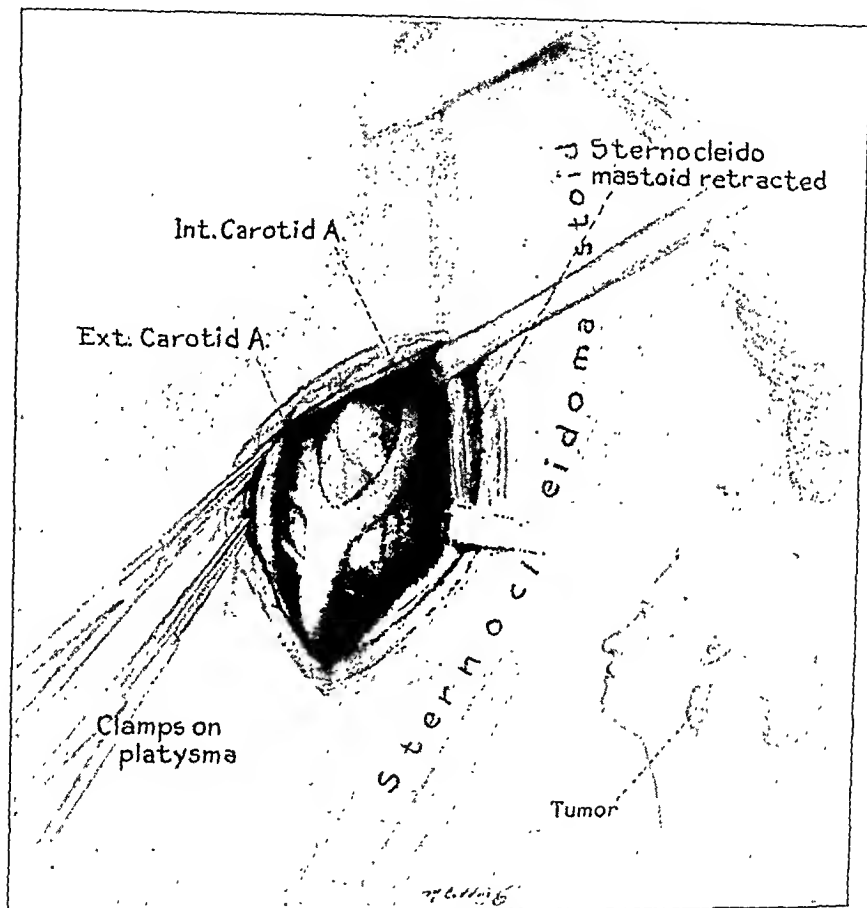


Fig. 20 (case 16).—Drawing of the operative field, with the tumor (cystic neurofibroma) lying deep in the cervical tissues and bulging the external carotid artery forward and the internal carotid artery laterally. The superior laryngeal nerve loops across the lower pole of the mass. A segment of the internal jugular vein has been resected to gain access to the tumor. (From *Ann. Surg.* 104:436 [Sept.] 1936).

laterally (fig. 20). A nerve, which seemed to be the vagus, was dissected off the mass laterally, and the superior laryngeal nerve, which had been pushed down the neck a long distance, was dissected off inferiorly. Eventually, by careful dissection, the upper pole was detached from the anterolateral surface of the



Fig. 21 (case 16).—*A*, external view of a cervical neurofibroma. *B*, cut surface of the cervical neurofibroma with extensive cystic degeneration. The specimen consists of little more than a shell, traversed by remaining trabeculae.

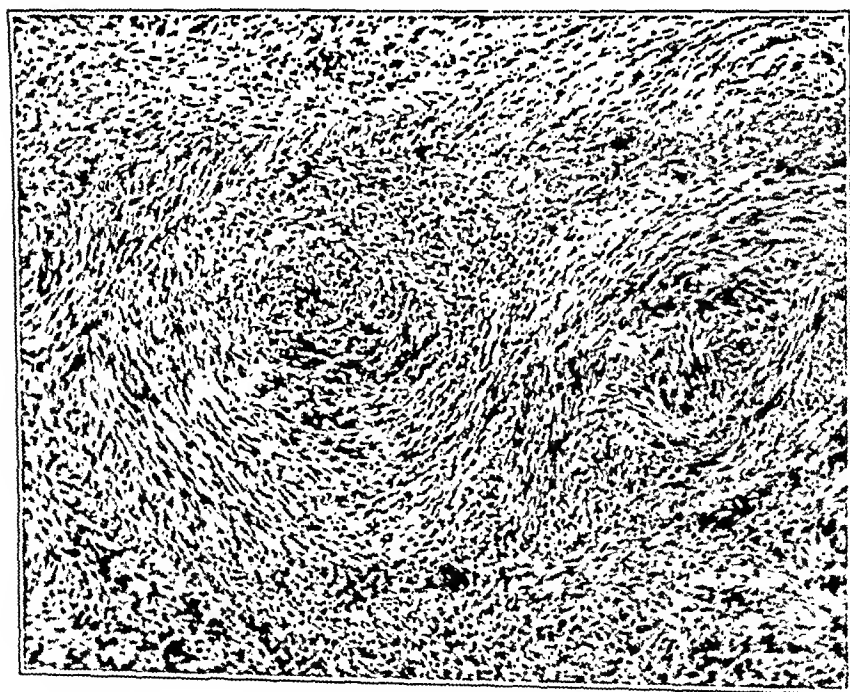


Fig. 22 (case 16).—Photomicrograph ( $\times 140$ ) from a small remaining portion of solid tissue (fig. 21 *B*) of a cystic cervical neurofibroma. Cells of mature type are seen in greatly interlacing bundles and whorls.

vertebral column, high up past the tonsil and close to the floor of the skull. (Presumably the mass arose from the anterior root of one of the upper cervical nerves.)

*Result.*—No paralysis or sensory loss could be detected after operation. There has been complete relief from symptoms, and up to the present time (October 1935) there is no evidence of recurrence.

*Pathologic Examination.*—The cystic mass removed was 6 cm. long, 3.5 cm. wide and 2.5 cm. thick. There was a continuous, tough, gray capsule (fig. 21A). When sectioned, in the greater portion of the specimen was a multilocular structure surrounded by a thin, fibrous wall about 1 mm. in thickness and traversed by fine, thin trabeculae and fibrous septums, dividing it into thin-walled cysts containing a clear, watery fluid. Toward one side of the specimen was a mass of dense gray to grayish white, rather firm substance, as shown in figure 21B.

Microscopically, the capsule as well as various portions of the trabecular tissue showed a dense fibrous structure with some whorl formation and interlacing of bundles (fig. 22) indicative of neurofibroma. There was little in the way of palisading of nuclei. No mitotic figures were seen. Throughout the solid tissue there were small cystlike spaces and other evidence of degeneration.

CASE 17.—A. R. S., a 36 year old woman, was seen on Nov. 30, 1922, complaining of a small nontender, slowly growing mass in the left side of the neck for eight years. At times when she moved her left arm there was a slight tingling sensation in the region of the left elbow. In the left side of the neck, just above the outer end of the clavicle, was a hard mass about 2.5 cm. in diameter, located beneath the skin and in the subcutaneous tissues. It was freely movable and could be pushed down under the clavicle.

*Operation.*—Dissection was carried down to the lateral trunk of the brachial plexus, from which the tumor arose. The mass was attached to the trunk between the origin of the suprascapular and that of the musculocutaneous nerve. The fibers of the lateral cord on reaching the tumor spread out diffusely over it, but the major number were grouped fairly definitely in a wide bundle along its under-surface. Enucleation was performed, leaving a rather broad band of fibers connecting the normal distal and the proximal portion of the nerve, which, as stated, went over the inferior aspect of the tumor.

*Result.*—After operation there was no area of anesthesia of the arm, and there was no evidence of any muscular weakness. The patient was not followed.

*Pathologic Examination.*—The specimen was irregularly shaped, smooth, pinkish gray and glistening and measured 2.5 cm. in diameter. On section there was a variegated appearance, some areas being rather firm, grayish white and glistening, while others were yellowish gray, soft and partially necrotic.

The microscopic picture was typical of a neurofibroma with many areas of degeneration and small cavity formation.

CASE 18.—M. G., a 23 year old man, was seen on May 31, 1933, complaining of a lump in the left side of the neck of four months' duration. For one year there had been frequent attacks of sharp pain in the dorsum of the left hand, over the region of the first metacarpal bone. He found that each attack of pain had been preceded by pressure of some sort in the left supraclavicular area. In the left supraclavicular region was a firm swelling about 5 cm. in diameter, which could be felt below as well as above the clavicle.

*Operation.*—Operation disclosed that the mass originated in the posterior cord of the brachial plexus (fig. 23). The tumor was completely excised along with

a segment of the cord from which it arose. The fragments of the posterior cord which had been severed were now reapproximated with silk sutures. The arm was immobilized in an airplane splint.

*Result.*—After operation the patient had, of course, complete paralysis of the radial and axillary nerves. In eight months the wrist drop was still complete, but in fourteen months there was fairly good dorsiflexion of the hand, and he suffered no real disability. In October 1934, seventeen months after operation, the patient had complete use of the arm and full power of every muscle. The area of anesthesia in the arm gradually disappeared, so that at the end of two years there was complete return of sensory function. At the present time, October 1935, there is no evidence of recurrence of the growth.

*Pathologic Examination.*—The well encapsulated, soft, oval tumor measured 4.7 cm. in length and 2.4 cm. in diameter. Branches of the posterior cord ran along in the capsule. The cut surface was light beige and had a slightly translucent, succulent and plexiform appearance, some areas showing mild cystic degeneration.

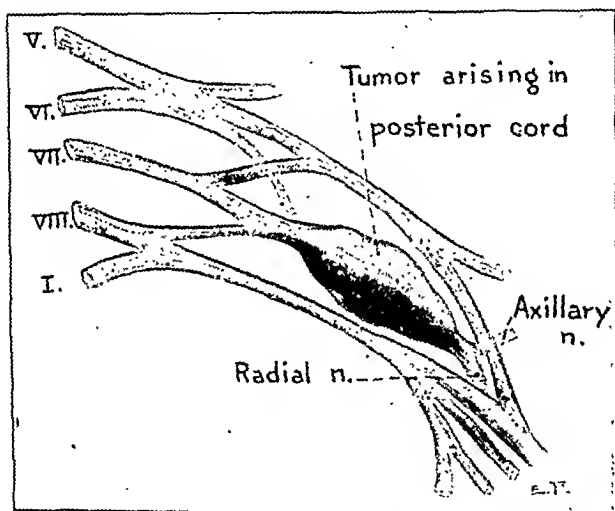


Fig. 23 (case 18).—Schematic drawing of the left brachial plexus to indicate the position of a malignant neurofibroma arising in the posterior cord. In this case the entire tumor and a segment of posterior cord were excised, followed by an end to end suture of the severed parts of the posterior cord. (Complete function of axillary and radial nerves subsequently restored.)

Microscopic examination showed a higher cellularity than that found in an ordinary neurofibroma. While many of the cells were of mature type and the nuclei were elongated and spindle shaped, there were other areas in which the nuclei were of a distinctly younger form. These were oval, at times almost rounded, having only a light chromatin network which was well dispersed (fig. 24). Many of the cells contained one or two small nucleoli. Mitotic figures were occasionally encountered. There was a rare suggestion of palisading of the nuclei. The cells often showed interlacing bundles and whorl formation. The relatively high cellularity of the tumor, the somewhat immature appearance of the cells and the presence of mitotic figures marked this neoplasm as having a distinctly



higher malignancy than the average neurofibroma. The changes, however, were not sufficient to make a diagnosis of neurofibrosarcoma, and we have listed it as a malignant neurofibroma to indicate the rate of growth. The microscopic picture justifies the complete removal of the mass with its nerve trunk, for dissecting such a growth from its nerve would certainly have led to recurrence.

CASE 19.—J. M. P., a 32 year old woman, entered the hospital on June 6, 1933, the chief complaint being intermittent pain in the left temporal and malar regions of the face of seven years' duration, and swelling in the left subtemporal region for two months. There was a continuation of the mass internally, for the left side of the pharyngeal vault protruded much more than the right. External aspiration produced 15 cc. of serohemorrhagic fluid. Sodium iodide was injected into this cavity, and roentgenograms (fig. 25) showed an irregular cyst from

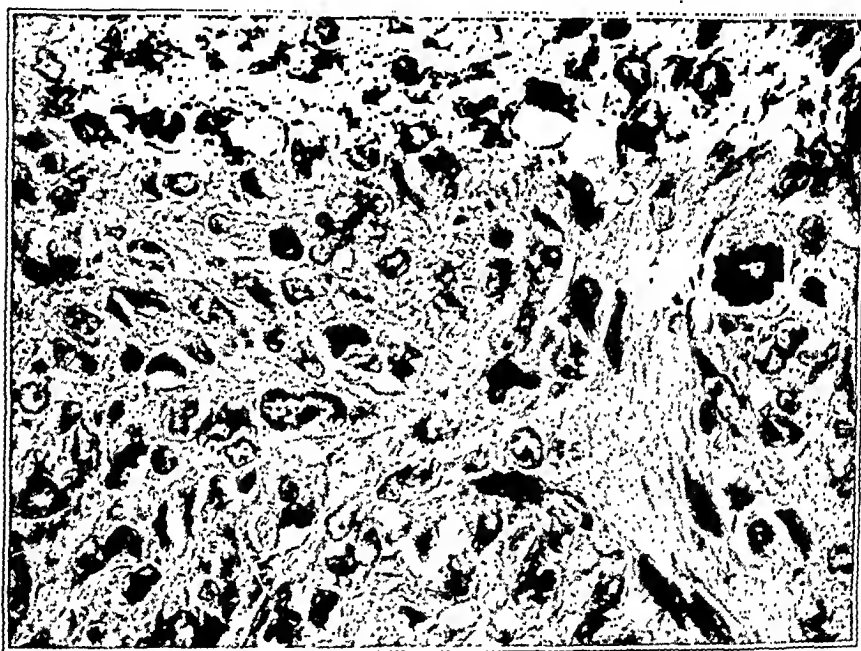


Fig. 24 (case 18).—Photomicrograph ( $\times 660$ ) of a malignant neurofibroma of the brachial plexus. There are fairly abundant cytoplasmic fibrillary processes and intercellular collagen. The nuclei have considerable variation in size and shape. One mitotic figure is seen toward the right.

3 to 5 cm. in principal diameters, lying largely in the lower portion of the temporal fossa, but also extending through the pterygopalatine fossa down into the soft palate. There was, in addition, intracranial extension through the great wing of the sphenoid bone, for the lateral and the posterior wall of the orbit were eroded.

*Operation* (June 9).—An incision was made over the mass externally, just above the left zygoma. The wound was deepened until a tough wall was encountered. A fragment of the wall of the cyst was removed for microscopic examination. The opened cyst was then thoroughly treated with sclerosing fluid, and the wound was packed open to allow for drainage. At the time of discharge from

the hospital on the fifth postoperative day, the pack had been withdrawn and the wound was beginning to heal.

*Pathologic Examination.*—The material removed from the wall of the cyst showed fibrous tissue with no evidence of neoplasm.

*Second Entry.*—The patient again entered the hospital on July 19, with the complaint of intermittent pain in the left malar and left temporal region. Since the previous admission there had been recurrence of swelling in the left malar, left temporal and left pharyngeal regions. There was a marked swelling extending well into the soft palate, which, on palpation, was fluctuant and cystic.

*Second Operation* (July 20).—The cystic portion of the mass in the soft palate was incised, and the heavy sac of the wall of the cyst was exposed. An attempt was made to free the lower portion of the cyst, but it seemed so firmly adherent to the surrounding structures that attempts at removal were abandoned. A portion of the wall of the cyst was then removed for further histologic study.

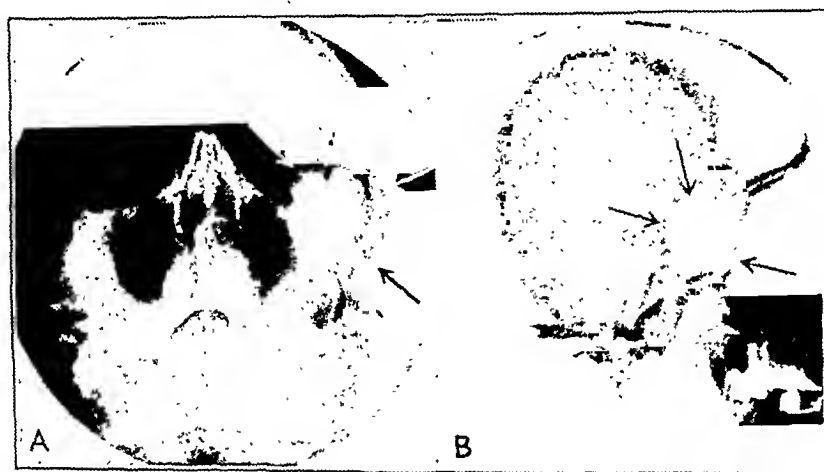


Fig. 25 (case 19).—A, postero-anterior view of the skull, showing a cystic neurofibroma of the temporal fossa (outlined by arrows) after the injection of sodium iodide. B, lateral view of the skull, indicating the position of the cystic neurofibroma of the temporal fossa (outlined by arrows) after the injection with sodium iodide.

A pack was placed in the palatine wound to allow for drainage, which subsequently continued for several weeks.

*Pathologic Examination.*—This portion of the wall of the cyst showed a fairly dense fibrous tissue with marked chronic inflammatory reaction. There was no evidence of neoplasm.

*Third Entry* (March 1934).—The patient had an infection of the upper respiratory tract, and subsequent to this there was a return and great increase in size of the swelling of the left side of the face. In addition, there was a mild exophthalmos on the left. The inside of the mouth showed a swelling on the left side of the roof, which was more pronounced than at any previous examination.

*Third Operation* (March 23).—An incision was made in the soft palate overlying the bulging cyst. A large fragment of the wall of the cyst was removed for microscopic study. Fluid in the cyst was purulent. The inner wall of the

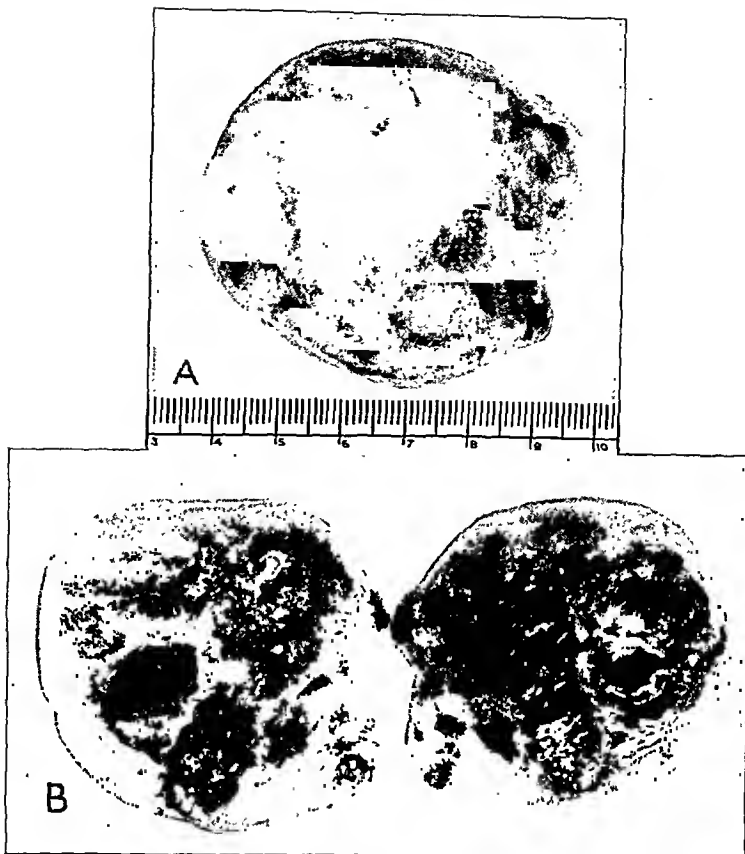


Fig. 27 (case 20).—*A*, external surface of a mediastinal neurofibroma. (Compare with figure 26.) *B*, cut surface of the neurofibroma, with multiple areas of hemorrhage and degeneration.

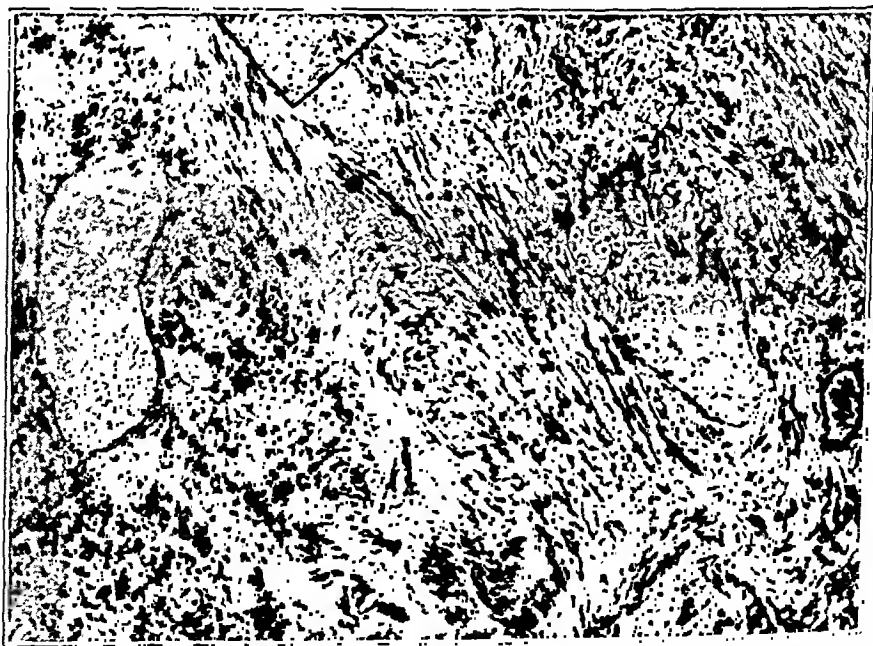


Fig. 28 (case 20).—Photomicrograph ( $\times 100$ ) of a mediastinal neurofibroma, with multiple areas of microcystic degeneration, many of which are filled with foamy, lipoid-laden phagocytes. The ruled-off zone at the top indicates the region shown in figure 29.

sional palisading of nuclei. There were prominent collections of large mononuclear cells with foamy cytoplasm, which stains for fat proved to be filled with lipoid droplets (fig. 29).

CASE 21.—S. S., a 27 year old woman, entered the hospital on Sept. 12, 1932, complaining of recurrent attacks of severe, sharp pain in the right side of the chest for five years. Examination showed an area of flatness to percussion, posteriorly on the right, from the seventh rib down to the base of the lung, extending from the spine out to the posterior axillary line. In this region the breath sounds were barely perceptible. Roentgen examination (fig. 30) disclosed a tumor about 10 cm. in diameter in the right side of the chest, posteriorly, which was apparently

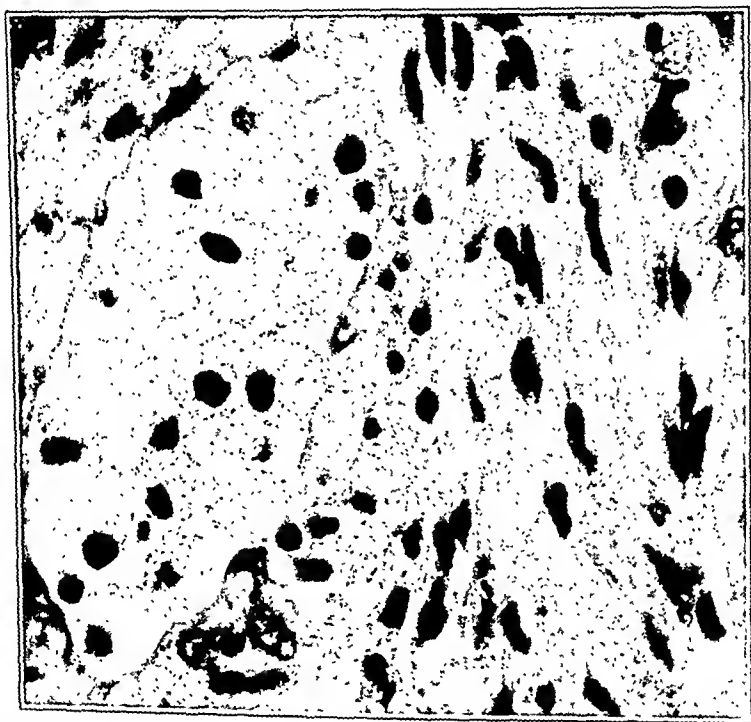


Fig. 29 (case 20).—Photomicrograph ( $\times 600$ ) of a mediastinal neurofibroma, with an area of cystic degeneration toward the left. This cyst is filled with large fat-laden phagocytes. (Compare with figure 28.)

separated from the heart, diaphragm and ribs. Fluoroscopy showed the mass to be adherent to the wall of the chest close to the spine. There was a definite thinning of the necks of the eighth and ninth ribs, close to the spine (pressure atrophy).

*Operation.*—Ether anesthesia was administered with a positive pressure Connell apparatus. A curvilinear incision was made on the posterior portion of the right side of the chest (fig. 31), extending from the level of the fifth rib downward and outward to the level of the tenth rib on the posterior axillary line. The ninth rib was excised from its angle forward to the breast and  $\frac{1}{2}$  inch (1.27 cm.) was removed from the eighth and tenth ribs in the region of their necks. The pleura was opened in the bed of the ninth rib, and the wound was spread



Fig. 30 (case 21).—Roentgenogram of the chest showing a large, round neurofibroma projecting into the right pleural cavity. The tumor arose from the eighth intercostal nerve.



Fig. 31 (case 21).—Postoperative photograph of a patient, indicating the position of surgical incision in removing a tumor of the eighth intercostal nerve. (Compare with figure 30.)

wide open. There was a firm, round tumor with a sessile base attached to the posterior wall of the thoracic cage, arising from the eighth intercostal nerve. The middle lobe of the right lung was adherent to the tumor, but this was readily separated by blunt dissection. The pleural covering of the tumor was then broken into, and the mass was removed by finger dissection after its blood supply had been ligated from the eighth intercostal vessels. Just before the last stitch in the pleural opening was tightened the lung was expanded by positive tracheal pressure, and all air was thus forced out of the pleural sac.

*Result.*—The patient made an excellent recovery; she has been free from complaint and evidence of recurrence for three years after operation.

*Pathologic Examination.*—The tumor weighed 326 Gm. and measured 8.8 by 7.6 by 7.8 cm. It was firm, well encapsulated and smooth. The cut surface was heterogeneous and gelatinous. Solid tissues were intermingled with small cavities, from 1 to 3 mm. in diameter, which were filled with a clear, watery fluid.

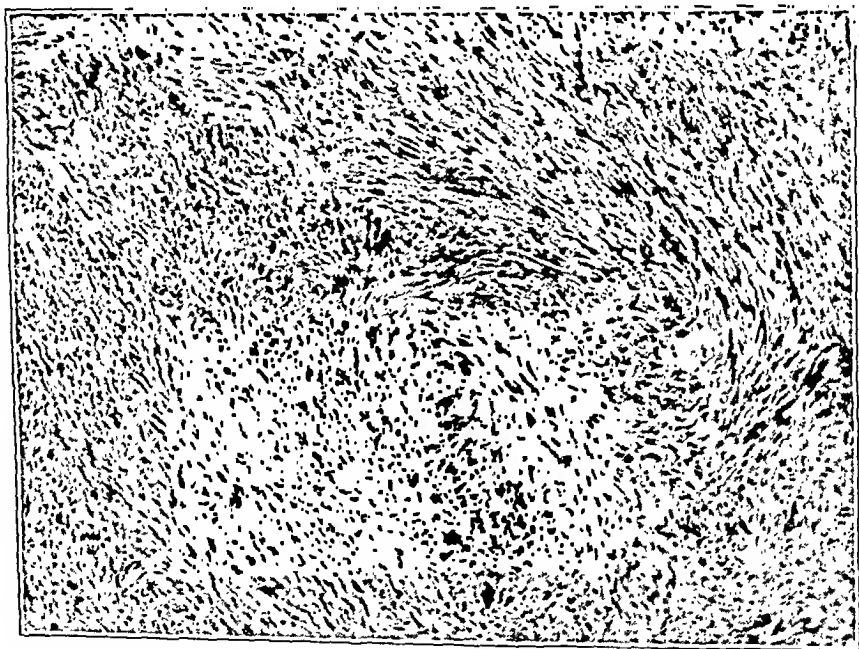


Fig. 32 (case 21).—Photomicrograph ( $\times 110$ ) of a neurofibroma of the intercostal nerve with interlacing fasciculi and whorls of mature connective tissue cells and fibers.

Microscopically, the tumor was fairly cellular and was typical of a neurofibroma. The cells were of a mature type and were arranged in bands and interlacing bundles (fig. 32). There was little variation in size and staining properties of the nuclei. Only slight tendency toward palisading of nuclei was present. Scattered areas showed considerable edema and degenerative change.

CASE 22.—F. C., a 30 year old woman, was first seen on Oct. 29, 1921, complaining of gradually increasing pain and swelling in the right axilla of twenty-one months' duration. During the last seven months the pain had radiated down the extensor surface of the arm, over the dorsa of the third, fourth and fifth fingers, to the right breast and also to the region of the scapula. Examination showed a

nodular mass, the size of a hen's egg, in the posterior portion of the right axilla, deeply situated and attached to the under-surface of the scapula, just above its inferior angle.

*Operation.*—An incision was made along the posterior axillary line and continued at right angles toward the midline of the back. The tumor was growing in the serratus magnus muscle, apparently arising from the long subscapular nerve. There was a forward extension of the mass toward the wall of the chest, so that the fifth rib had to be denuded of its periosteum in removing all of the visible growth. The lower portion of the scapula, the underlying mass and the adjacent musculature were all resected *en masse*. The subscapularis and infraspinatus muscles were then sewed together over the cut edge of the scapula, and the stump of the muscles was then sewed to the cut edge of the latissimus dorsi.

*Result.*—The patient received postoperative roentgen irradiation over the operative site. She was temporarily relieved, but there was recurrence of pain beginning six months after operation. Five years later the neoplasm had infiltrated the brachial plexus and greatly invaded the upper portion of the thoracic cage. The patient was subsequently lost track of but died in another hospital in May 1934, after exhibiting massive extension of the neoplasm into the brachial plexus and thoracic cavity.

*Pathologic Examination.*—The nonencapsulated tumor, measuring 7 by 2.5 by 2 cm., infiltrated the adjacent musculature. It was firm and on cross-section presented a light gray substance composed of dense interlacing bands of fibrous tissue.

Microscopically, there were elongated spindle cells in interlacing bundles, cut at different angles. The nuclei were long, ovoid and vesicular and had one or two small nucleoli. Mitotic figures were fairly easily found. The scanty cell cytoplasm trailed out into fine fibrillar structures. The growth had the general appearance of a slowly growing fibrosarcoma, but because of the tendency toward waviness of cells and a suggestion of palisading it was definitely felt to be a malignant tumor of the nerve sheath. The degree of malignancy was insufficient to allow it to be termed a neurofibrosarcoma, but because of the increased rate of growth and subsequent regional extension seen clinically, we have called this tumor a malignant neurofibroma.

CASE 23.—R. L. A., a 41 year old woman, entered the hospital on Jan. 8, 1917, complaining of a tender, small lump in the perineum, which had gradually increased in size over a period of seven years. Just to the right side of the central point of the perineum there was a small, firm, tender mass from 2 to 3 cm. in diameter. It did not bulge into the vagina or rectum.

*Operation.*—Operation disclosed irregular, chainlike, firm and encapsulated masses partly on and partly beneath the deep fascia. These masses were easily dissected free from the surrounding tissues. Small strands of nerve (perineal) were noted entering and leaving these.

*Result.*—When the patient was last seen, in 1930, there was no evidence of recurrence.

*Pathologic Examination.*—The specimen consisted of five small discrete circumscribed tumors arranged in a chain and held together by a nerve trunk which passed between them. The largest of these measured 3 by 1.5 by 0.8 cm. On section they were gray and slightly moist, and each was surrounded by a thin capsule.

Microscopic examination of all these masses showed them to be histologically of similar tissue and all representing typical neurofibromas. At the periphery of

the nodules some nerve fibers of the nerve trunks connecting these masses could be identified, but there was no evidence of Recklinghausen's disease.

CASE 24.—A. K., a 32 year old man, was seen on Oct. 17, 1932, having had a hard, superficial, flattened, nontender mass on the midposterior region of the right thigh for six years.

*Operation.*—An elliptical portion of skin, including the central mass, was excised.

*Result.*—The patient was not followed.

*Pathologic Examination.*—In the center of the portion of skin was an area 1.5 cm. in diameter which was raised 0.5 cm. above the level of the surrounding surface of the skin. On section this central pearly white mass was seen to be 1.2 cm. in thickness. It was nonencapsulated but was covered externally by the epidermis and projected down into the subcutaneous fat.

Microscopic examination showed a typical neurofibroma lying in and partially replacing the corium, with interlacing bundles and whorls of mature connective tissue cells laying down a moderate amount of collagen. There was little palisading of nuclei. Small nerves were seen coursing at the periphery of the nonencapsulated tissue.

CASE 25.—W. P., a 33 year old man, was seen in July 1933, complaining of a small, tender lump in the skin over the lateral aspect of the upper part of the left arm, which had been present for several years.

*Operation.*—A small cutaneous mass with surrounding skin was excised.

*Result.*—The patient was not followed.

*Pathologic Examination.*—In the center of the excised skin there was a small, nonencapsulated but fairly discrete mass 5 mm. in diameter, covered externally by epidermis and inferiorly by subcutaneous fat. On cut section this central mass was firm, elastic and pale yellowish gray.

Microscopic examination showed a typical nonencapsulated neurofibroma lying within the corium and replacing the appendages of the skin. It was rather cellular, but there was no evidence of malignancy. Long interlacing bundles and whorl formations were seen, and some mild palisading of nuclei was present. At the periphery of this neurofibroma numerous small cutaneous nerves appeared.

#### SUMMARY

Twenty-five representative cases of benign or malignant tumor of the sheath of a peripheral nerve, unassociated with Recklinghausen's disease, are reported. The most frequent sites for the neoplasms are the posterior surfaces of the legs, the anterior surfaces of the arms and neck. The tumors vary greatly in size and have a marked tendency to cystic degeneration. The benign form is easily separated from the nerve trunk, which can be left intact. The malignant tumor infiltrates and cannot be separated from its nerve. In dealing with the slowly growing neurofibroma, it is justifiable to peel it off from the nerve, but with those showing a more rapid rate of growth a portion of nerve should also be resected, followed by end to end suture of the nerve. Operations on sarcoma of the nerve sheaths should be radical, and in the absence of metastases, early amputation of the involved limb gives the best chance of cure. Radium or roentgen irradiation of the malignant forms has been almost universally a disappointing procedure.



# EFFECT OF POSTERIOR PITUITARY EXTRACTS ON MOTILITY OF THE GASTRO-INTESTINAL TRACT

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The numerous attempts to determine the effect of extracts of the posterior lobe of the pituitary gland on the motility of the gastro-intestinal tract have occasioned conflicting and contradictory observations. Having at our disposal a number of patients and several trained dogs with intestinal fistulas, we attempted a further elucidation of this problem.

The literature on this subject is extensive and can be summarized only briefly here.

## EFFECT OF POSTERIOR PITUITARY EXTRACTS ON EXCISED STRIPS AND ISOLATED SEGMENTS OF THE INTESTINE

Whereas one might suspect a priori that the effect of posterior pituitary extracts on extirpated intestinal strips could be easily determined, in actual practice the problem is far from solved.<sup>1</sup>

The species of the experimental animal,<sup>2</sup> the  $p_H$  of the bath,<sup>3</sup> the presence of histamine or other impurities,<sup>4</sup> and the depressor antiseptics

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Several preliminary experiments were done by Dr. E. Rosenman.

From the Department of Gastro-Intestinal Physiology of the Michael Reese Hospital.

Aided by a grant from the Committee on Scientific Research of the American Medical Association.

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2. Sollmann, T. H.: *Glandular Therapy: Pharmacology of the Pituitary Gland*, J. A. M. A. **83**:1683 (Sept. 13) 1924.

3. Gruber, C. M.: One of the Factors Governing the Relaxation of Non-Striated Muscle (Intestine) by Commercial Pituitary Extract, *J. Pharmacol. & Exper. Therap.* **30**:73, 1927.

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contained in commercial extracts<sup>5</sup> serve to explain the varying and contradictory results.

Further, it has been reported that the oxytocic principle of the pituitary gland counteracts the pressor hormone<sup>6</sup> and that the degree of tonus of the intestine determines the type of reaction.<sup>7</sup>

#### REVIEW OF EXPERIMENTAL WORK REPORTED IN THE LITERATURE

*Cat.*—Of one hundred anesthetized or pithed cats that received injections of solution of posterior pituitary, some of which were given hourly administrations of the drug for an entire day, only two defecated.<sup>8</sup> Other workers have stated that no augmented colonic activity could be detected fluoroscopically in cats in response to posterior pituitary extract.<sup>9</sup>

*Rabbit.*—The rabbit is the only animal in which most observers have detected increased peristalsis or defecation.<sup>10</sup> However, inhibition has been reported.<sup>11</sup>

*Dog.*—Inhibition: The various descriptions of the intestinal response of the dog to posterior pituitary preparations are largely inconsistent.

5. Roth, G. B.: Pituitary Standardization: The Relative Value of Infundibular Extracts Made from Different Species of Mammals and a Comparison of Their Physiological Activity with That of Certain Commercial Preparations, United States Public Health Service, Hygienic Laboratory, Bulletin 109, December 1916.

6. Elmer, A. W.; Ptaszek, L., and Scheps, M.: Die Wirkung des Vasopressins und Oxytocins auf die Behandlung der Darmlähmung (Ileus Paralyticus) mit Vasopressin, *Klin. Wchnschr.* 9:1765, 1930.

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8. MacDonald, A. D.: The Action of Pituitary Extracts on Intestinal Muscle, *Quart. J. Exper. Physiol.* 15:191, 1925.

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10. (a) Fodera, F. A., and Pittau, L.: Studi sull'hypophysis cerebri, *Pathologica* 1:269, 1909. (b) Franchini, G.: Die Funktion der Hypophyse und die Wirkungen der Injektion ihres Extraktes bei Tieren, *Berl. klin. Wchnschr.* 47:670, 1910. (c) Bell, W. B.: The Pituitary Body and the Therapeutic Value of the Infundibular Extract in Shock, Uterine Atony and Intestinal Paresis, *Brit. M. J.* 2:1609, 1911. (d) Ott, I., and Scott, J. C.: Action of Animal Extracts upon Intestinal Movements, *Am. Med.* 17:154, 1911. (e) Katsch, G., and Borchers, E.: Beiträge zum Studium der Darmbewegungen, *Ztschr. f. exper. Path. u. Therap.* 12:277, 1913. (f) Zondek, B.: Der Einfluss des Hypophysenextraktes auf die Peristaltik, *Arch. f. d. ges. Physiol.* 180:38, 1920. (g) Gaddum, J. H.: Some Properties of the Separated Active Principles of the Pituitary (Posterior Lobe), *J. Physiol.* 65:434, 1928.

11. Shamoff, V. N.: Concerning the Action of Various Pituitary Extracts upon the Isolated Intestinal Loop, *Am. J. Physiol.* 39:268, 1916.

More observers have perceived inhibition of the intestine in response to solution of posterior pituitary or pitressin in unanesthetized,<sup>12</sup> anesthetized<sup>13</sup> or pithed dogs<sup>14</sup> and in dogs with intestinal obstruction.<sup>15</sup> Again, the hyperperistalsis evoked by insulin has been reported as being inhibited by the several extracts of the posterior lobe of the pituitary gland.<sup>16</sup>

*Dog.*—Stimulation: The minority of workers describe excitation of the bowel in response to posterior pituitary extract, but the type of excitation produced has varied distinctly and has apparently been determined in some measure by the presence or absence of anesthesia.

In anesthetized dogs different observers have reported (*a*) an increase in the tonus of the small intestine but a decrease in the tonus of the large bowel<sup>13b</sup> and (*b*) pure excitation.<sup>6</sup>

In unanesthetized dogs with fistulas, solution of posterior pituitary, pitressin and pitocin have evoked a transient diminution in tonus and contraction of the ileum, succeeded by high tonus and intensified peristalsis and occasionally by actual tetanus.<sup>17</sup> Carlson<sup>18</sup> has described an initial augmentation of the hunger contractions. It is particularly interesting that in the unanesthetized dog the pressor and the oxytocic principles have been reported as provoking defecation, fluoroscopy

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12. Ginsburg, H., and Tumpowsky, I.: Contributions to the Physiology of the Stomach: I. Studies on the Control of Hunger by Drugs, *Arch. Int. Med.* **22**:553 (Nov.) 1918. Quigley, J. P.; Highstone, W. H., and Ivy, A. C.: Action of Morphine, Papaverine, Atropine, Pilocarpine, Pituitrin and Pitressin on Intestinal Propulsive Activity Determined in the Unanesthetized Dog by the Bolus Method, *J. Pharmacol. & Exper. Therap.* **51**:308, 1934.

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16. Quigley, J. P., and Barnes, B. O.: Action of Insulin on the Motility of the Gastro-Intestinal Tract: VI. Antagonistic Action of Posterior Pituitary Lobe Preparations, *Am. J. Physiol.* **95**:7, 1930.

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18. Carlson, A. J.: *The Control of Hunger in Health and Disease*, Chicago, University of Chicago Press, 1916.

demonstrating an increased motility of the intestinal tract (only with the pressor substance) which could not be detected by the balloon method.<sup>19</sup>

*Man.*—Most of the data pertinent to man have been gathered by surgeons, since solution of posterior pituitary and pitressin are used widely in the treatment of paresis of the intestinal tract.

The isolated human appendix is reported to undergo an increase in tone on the addition of pituitary extract to the tissue bath.<sup>20</sup> In normal man the reported observations vary from an inconstant gastric motor response and either no effect on or relaxation of the intestines<sup>21</sup> to a distinct increase in peristalsis.<sup>6</sup>

Patients on whom colostomy or ileostomy has been performed have been reported to respond to the subcutaneous injection of pituitary extracts with an increase in the intestinal activity.<sup>13c</sup>

In the presence of atony of the intestinal tract, solution of posterior pituitary or pitressin may yield borborygmi, release of flatus and defecation.<sup>22</sup> Other surgeons have described an increase in tone and no stimulation of peristalsis as the effect of the drugs.<sup>23</sup>

19. Melville, K. I., and Stehle, R. L.: The Actions of Pituitary Preparations (Posterior Lobe) upon the Intestines of the Dog, *J. Pharmacol. & Exper. Therap.* **50**:165, 1934.

20. Cross, D. G. T. K.: The Action of Physostigmine and Pituitrin, *Brit. M. J.* **1**:9, 1924.

21. Pancoast, H. K., and Hopkins, A. H.: The Action of Pituitrin upon the Gastro-Intestinal Tract of Man, *New York M. J.* **105**:289, 1917.

22. Bidwell, L. A.: Investigation into Effect of Pituitary Extract on Bowels After Abdominal Operations, *Clin. J.* **38**:351 (Sept. 6) 1911. Klotz, R.: Pituitrintherapie bei Peritonitis, *München. med. Wchnschr.* **59**:2047, 1912. Houssay, B. A., and Beruti, J.: Sur l'emploi de la médication hypophysaire comme agent entérocinétique, *Presse méd.* **21**:613, 1913. Duffy, R.: Pituitary Extract in Post-Operative Intestinal Stasis, *New York M. J.* **101**:72, 1915. Young, H. H.: The Value of Drugs in Urology, *J. A. M. A.* **77**:1327 (Oct. 22) 1921. Pate, J. C.: The Use of Pituitrin in Abdominal Surgery, *J. M. A. Georgia* **11**:455, 1922. Mayer, A.: Zur Behandlung postoperativer Darmlähmungen, *München. med. Wchnschr.* **71**:931, 1924. Schmidt, H.: Vergleichende Untersuchungen über die Darmwirkung des Hypophysins, *Zentralbl. f. Chir.* **52**:121, 1925. Vogt, E.: Die intravenöse Hypophysinkochsalzinfusion zur Behandlung der postoperativen Darmlähmung, *München. med. Wchnschr.* **73**:1509, 1926. Ward, G. G.; Lyon, E. C., and Bemis, G. G.: Clinical Results Obtained with Oxytocin and Vasopressin, the Recently Isolated Principles of Pituitary Extract, *Am. J. Obst. & Gynec.* **16**:655, 1928. Black, C. V.: Pitressin in Surgery, *J. Kansas M. Soc.* **35**:216 (June) 1934. Fervers: Hyphophysenextrakt-Injektion bei Ileus und nach Laparatomie, *Med. Klin.* **18**:438, 1922. Elmer, Ptaszek and Scheps,<sup>6</sup> Bell.<sup>10c</sup>

23. Potter, P. C.: The Relation of Post-Operative Paralytic Ileus to Mortality in Acute Appendicitis, *Ann. Surg.* **99**:985, 1934; Acute Diffuse Peritonitis Following Acute Appendicitis with a Report of Twenty-Five Cases, *S. Clin. North America* **14**:379 (April) 1934. Potter, P. C., and Muller, R. S.: Posterior Pituitary Extract in the Prevention of Post-Operative Intestinal Distention, *Ann. Surg.* **86**:364, 1932.

Pituitary extracts have been employed successfully in the treatment of constipation.<sup>24</sup>

In a case of poisoning due to the ingestion of chenopodium, intravenous administration of 600 cc. of saline solution plus six ampules of pituitary extract induced defecation.<sup>25</sup>

Cushing<sup>26</sup> reported an increase in the tone of the gastro-intestinal tract and violent contractions after the intraventricular administration of solution of posterior pituitary double U. S. P. strength, and a diminution in tone after intravenous injection.

#### METHODS

The balloon method of Carlson<sup>18</sup> and recording water manometers were used. The patient lay comfortably in bed, with a signal button in hand to indicate pain, hunger, etc. Pitressin, pitocin and solution of posterior pituitary were the drugs used, the injections being given intramuscularly.<sup>27</sup>

Dogs with gastro-intestinal fistulas were selected for their docility and training. They lay quietly on a soft pad, with eyes blindfolded, for several hours, undisturbed by intravenous or intramuscular injections.

Since it has been thought possible that diet may influence the response of the organism to the extract,<sup>28</sup> dog 1 was fed for two weeks a vegetable-carbohydrate diet, a meat-carbohydrate diet and a mixed diet, respectively. With this exception, all other tests involved no dietary restrictions.

The acute experiments on the dog were performed with the animal under ether anesthesia (one under narcosis with pentobarbital sodium). Blood pressure was recorded with a mercury manometer; the motility of the gastro-intestinal tract with balloons and water manometers.

In several acute experiments on animals, a one stage bilateral adrenalectomy was performed, and of these experiments none is included here in which the blood pressure sank below 80 mm. of mercury.

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24. Sophian, A.: Pituitary Extract (Posterior Lobe), J. Missouri M. A. **27**:384, 1930. Carnot, P., and Terris, E.: Action des extraits post-hypophysaires sur le peristaltisme intestinal et sur la constipation, Paris méd. **1**:333, 1926.

25. Vogt, E.: Ueber die Verwendung der intravenösen Hypophysenkochsalzinfusion bei der Behandlung der Vergiftungen durch Oleum chenopodii, Klin. Wchnschr. **5**:1638, 1926.

26. Cushing, H.: Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 106.

27. The pitressin and pitocin were supplied by Parke, Davis & Co., the solution of posterior pituitary by Wilson Laboratories and the solution of posterior pituitary double U. S. P. strength by Eli Lilly & Co.

28. Abderhalden, E., and Wertheimer, E.: Studien über den Einfluss der Ernährung auf die Wirkung bestimmter Inkretstoffe, Arch. f. d. ges. Physiol **205**:559, 1924; **206**:451, 1924; **207**:222, 1925; **213**:328, 1926. Degener, L. M.: Studies on the Effect of Diet on the Weight of the Hypophysis and Thyroid Gland of the Albino Rat, and on the Action of Their Extracts on the Isolated Small Intestine, Am. J. Physiol. **60**:107, 1922.

## RESULTS

*Man* (table 1).—Sixteen tests were performed on ten subjects. Nine of the patients had an intestinal fistula, and one subject was a normal young woman. All were in excellent physical condition at the time of the tests, their respective operations having been completed months, and in some instances years, before. Those on whom resection for colonic carcinoma had been performed may have had metastases at the time of these experiments, but, clinically and subjectively, their condition was good. In the patients with ulcerative colitis, either the diseased segment of bowel had been extirpated or a simple ileostomy had allayed symptoms. The balloon was passed along the fistula into the uninvolved portion of the intestine and held in place by adhesive tape attached to the skin.

Table 1 indicates that the human ileum was inhibited by pitressin only once. In ten tests pitressin augmented the toms of the ileum or colon, and in three other instances it elicited no response.

The change in the amplitude of the contractions of the intestine paralleled the alteration in tone. Thus, in twelve trials, ileal and colonic contractions were considerably increased by pitressin, and in only one case was this effect not obtainable.

The stomach of the normal subject (no. 10) failed to respond in any way to pituitary extract in the doses employed.

Particularly significant is the datum that in six tests pitressin caused colicky pain.

In several instances pitressin elicited maximal intestinal contractions, which at least once culminated in subcutaneous of the ileum (no. 6). Further, moderately high contractions appeared in another four tests.

The latent period was usually short: from one tenth of a minute to thirteen minutes, with an average of five minutes. The duration of contractions induced by pitressin varied from six to thirty minutes. In four subjects powerful contractions extruded the balloon from the fistula. Occasionally the experiments were interrupted because of discomfort of the patient. Defecation occurred through the stoma nine times in fourteen trials. In one patient evacuation of the bowel in response to pitressin occurred five times in the course of one experiment and again three times at a subsequent examination.

Chart 1 depicts the result of the first test on patient 8 (table 1). It demonstrates the strong intestinal contractions produced by 0.5 cc. of pitressin administered intramuscularly, which expelled the balloon from the fistula and terminated in defecation.

Throughout the latent period, the toms and motility of the colon were depressed, and after the period of specific response this condition reappeared. This was commonly observed in the majority of the experiments in man and in the dog in which pitressin produced a motor effect.

The short and transient contraction, on reintroduction of the balloon, results from the initial distention of the intestine. For this reason, every injection of a drug was preceded by a control period of not less than thirty minutes. When no regularity in motility was observed, resort was taken to longer control periods, or occasionally the particular experiment was abandoned.

*Unanesthetized Dogs.*—Three dogs were used, all manifestly in excellent health. Dog 1 was served in succession a vegetable, a meat and a mixed diet, as described previously, but the individual results of these periods are not recorded separately, since no significant differences were obtained.

TABLE 1.—Results of Motor Response of the Intestines to Pitressin

Patient				Location of Fistula in	Disease	Pitres- sin, 1 Cc. Intra- muscu- larly	Before Injection		Contra- ctions	After Injection					
No.	Initials	Sex	Age				Tonus	Contra- ctions		Tonus	Contractions	Latent Period	Duration	Pain	Defecation, Minutes After Injection
1	A. L.	F	34	Ileum	Ulcerative colitis	0.5	Small waves	Small	Small	Increased	Maximum	2	29	Cramplike	13
2	B. S.	M	27	Ileum	Ulcerative colitis, colectomy	1.0	Small waves	Small	Small	Slight decrease	Slight decrease	2	30	..	..
3	H. K.	M	23	Ileum	Ulcerative colitis	1.0	No waves	None	None	Increased	Maximum	5	30	..	15
4	B. D.	M	16	Ileum	Ulcerative colitis	1.0	Small waves	Small	Small	Increased	Medium	13	Balloon out	..	13
5	N. G.	F	22	Ileum	Ulcerative colitis	1.0	No waves	Small	Small	Waves	Medium	3	20	..	..
6	G. I.	M	65	Ileum	Ulcerative colitis	1.0	No waves	Small	Small	No waves	Small	..	..	..	..
					Cancer of rectum	1.0	Medium waves	Medium	Medium	No change	Medium	3	25	..	8
										No change	At first, then medium, then subtetanle	7	35	..	19-21-25-29-35
7	R. T.	M	60	Colon	Cancer of rectum	1.0	Small waves	Small	Small	Increased	High	13	16	Colicky	15-17-21
8	L. D.	M	43	Colon	Cancer of rectum	0.5	Medium waves	Medium	Medium	Increased	Maximum	1/10	Balloon out	+++	2
						0.5	Small waves	Small	Small	Medium waves	High	5	Balloon out	++	..
9	L. L.	F	30	Colon (sigmoid)	Ulcerative colitis	1.0*	Small waves	Small	Small	Medium waves	High	7	6	..	..
						0.5	No waves	Medium	Medium	Increased	Maximum	3	Balloon out	+++	4
10	D. M.	F	21	Stomach balloon swallowed	Normal	1.0	No waves	Small	Small	Increased	High	5	25	+++	14
					student		Small waves	Small	Small	Small waves	Small	..	..	..	..
						1.0	Small waves	.....	.....	Small waves	.....	..	..	..	..

\* Solution of posterior pituitary; Parke, Davis &amp; Co.

In this dog, pitressin and pitocin either decreased the tone and the amplitude of the contractions of stomach and jejunum or had no effect. Only once was a slight rise of gastric tonus observed (solution of posterior pituitary). The latent period for depression varied between one and eight minutes (once twenty minutes), with an average of three and one-half minutes. The duration of the depression varied from eleven to forty-five minutes, averaging twenty-one minutes.

However, in one test, after the use of surgical solution of posterior pituitary double U. S. P. strength the stomach underwent complete inhibition of tonus and motility for sixty minutes and complete inhibition of hunger contractions for one hundred and twenty minutes (a total of three hours). At the time of injection, hunger contractions prevailed. From a two months' study of this dog's hunger contractions, we knew their periodicity, and no period of relative quiescence between hunger contractions ever lasted longer than thirty minutes.

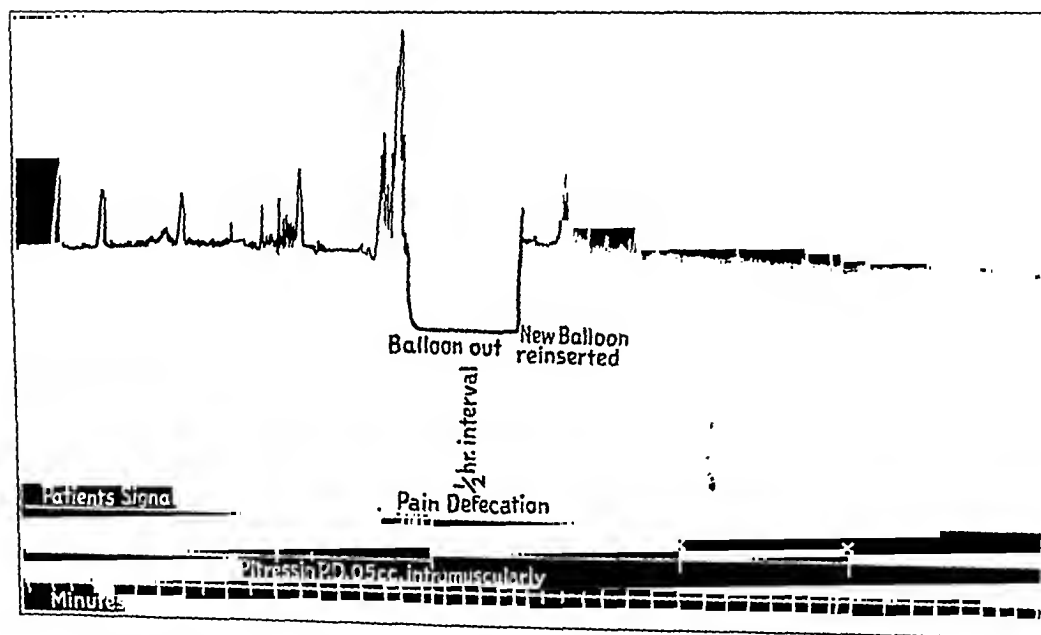


Chart 1.—Response of human colon to intramuscular injection of 0.5 cc. of pitressin.

In general, both the stomach and the jejunum behaved identically as to the latent period and the duration of the response.

Dogs 2 and 3 received only pitressin.

Dog 2 received seven injections of the drug, three proving entirely negative in effect, whereas the other four evoked ileal depression (latent period, from one to three minutes; duration, from eleven to nineteen minutes).

Dog 3 was easily the most placid and docile of the three animals. Here every experiment, although not every injection, yielded a distinct and frequently marked increase in tonus and in the number and height of contractions.

In this dog, six of eight injections of pitressin produced positive motor effects in the stomach and ileum (latent period, from one to eight minutes; duration, from four to thirty-two minutes). This animal was the only one that defecated in response to pitressin (four times).



In most instances a depression of motility and frequently of tonus appeared during the latent period. In three experiments tetanic contractions of the ileum developed, succeeded by strong contraction waves, which then passed into a long period of depression or complete inhibition of motility and tonus. Chart 2 illustrates a typical experiment with this dog.

We considered it especially significant that pitressin consistently stimulated the motility of the gastro-intestinal tract in only dog 3, which was so thoroughly unruffled that even defecation or disturbances in the room about her constituted insufficient reason for movement.

The other two dogs, although well trained and quite unmindful of the intravenous injections, could be disturbed by extraneous noise. And thus the possibility was suggested that at least some component of the inhibition induced by pitressin in these dogs might represent sensory or adrenal inhibition.

Accordingly, the investigations were extended to include eight etherized dogs and four acutely adrenalectomized dogs.

*Anesthetized Dogs.*—In this group, forty-six injections of pitressin yielded increased tonus and in the height of the contractions of the stomach, jejunum, ileum or colon (seven times); depression of tonus and amplitude of the contrac-

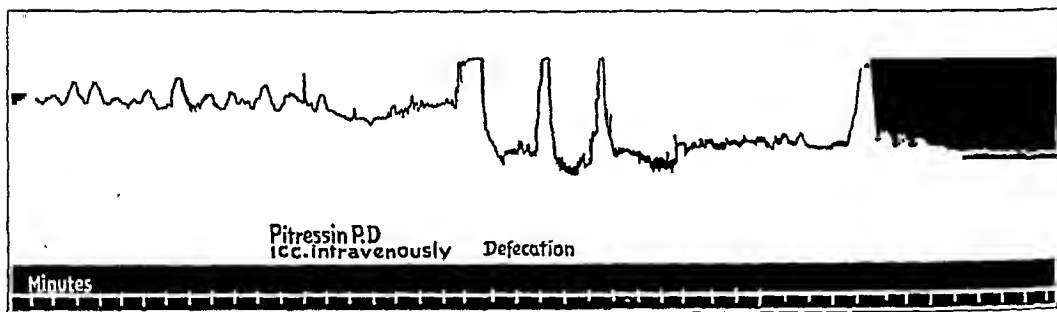


Chart 2.—Response of ileum of dog no. 3 to intravenous injection of 1.0 cc. of pitressin.

tions (seven times), and no effect (thirty-two times). Pitocin and solution of posterior pituitary were entirely ineffectual, never eliciting the depression that sometimes occurred in unanesthetized dogs.

Unlike the response of the unanesthetized dogs (nos. 1 to 3, table 2), the stimulating effect obtained here with pitressin did not occur consistently in any one dog or in any segment of bowel. A casual comparison of these data with the response of the unanesthetized dogs 1 and 2 indicates that the gastro-intestinal tract of the narcotized dog responded more frequently to pitressin with an increase in tonus and contractions.

*Adrenalectomized Dogs.*—Pitressin had practically no effect on the adrenalectomized animals. Their gastro-intestinal tract remained atonic, the result possibly of the section of many sympathetic fibers and trauma to the celiac ganglion during adrenalectomy.

#### COMMENT AND CONCLUSIONS

The consistency with which pitressin is effective in producing an increase in the intestinal activity in man is remarkable. The response in dogs is hardly as unequivocal.

TABLE 2.—Experiments on the Motility of the Stomach and Intestine  
(Balloon Method)

[illegible]

However, it was demonstrated that in a well trained and especially placid dog (no. 3, table 2) pitressin evoked the same response as in man: a marked increase in tonus and in the height and frequency of the contractions, tetanus and defecation. The other two dogs (nos. 1 and 2) were certainly well trained but more easily perturbed by external movements and noise, and for them pitressin proved to be ineffectual. This may indicate that the susceptibility of a dog to external disturbing stimuli may modify the action of the drug.

The experiments performed with the dogs under ether anesthesia (table 2, no. 4 to 11) partly corroborate this assumption, because here the incidence of a positive response of the gastro-intestinal tract to pitressin was greater than that which occurred in the unanesthetized dogs. (nos. 1 and 2).

The experiments on adrenalectomized dogs do not demonstrate much. The trauma to the celiac plexus and to the sympathetic fibers may partly explain the negative results. Hoskins and McPeck,<sup>29</sup> in an attempt to determine the relationship between the pressor effect of solution of posterior pituitary stimulation of the adrenal glands, reached a similar conclusion. Yet it should be remembered that many other stimuli may inhibit the canine intestine, and therefore a number of well conceived experiments will be necessary to solve this problem.

The foregoing results in man demonstrate that pitressin (solution of posterior pituitary in one subject) consistently evokes the motility of the intestinal tract and frequently elicits violent contractions, tetanus, colicky pain and defecation. This confirms recent work performed on a smaller group of patients.<sup>13c</sup>

The slow, tonic contractions of the intestine observed by surgeons<sup>23</sup> when solution of posterior pituitary was given in the course of a laparotomy were never visible in our records. Possibly such results depend on the acute surgical procedure as well as on the handling of, and the access of cool air to, the viscera.

In all experiments on man and on the dog we were unable to detect a constant correlation between the preceding state of tonus and contractions and the response to the extracts of the posterior lobe of the pituitary gland. Nor could we establish the existence of an antagonism between pitressin and pitocin.

In view of our data, it is somewhat difficult to interpret the failure of fluoroscopy to detect motility.<sup>21</sup> Of course we are aware of the profound differences between the balloon method and fluoroscopy. But, if anything, the former method is less sensitive and gives less information

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29. Hoskins, R. G., and McPeck, C.: Is the Pressor Effect of Pituitrin Due to Adrenal Stimulation? *Am. J. Physiol.* **32**:241, 1913.

than the latter, so that positive results obtained with the balloon method are therefore particularly significant (Carlson).<sup>18</sup>

The violent contractions in several experiments in which only 0.5 cc. of pitressin was given intramuscularly (table 1, patients 1, 7, 8 and 9) warn the surgeon to be cautious in the use of this drug, particularly in those instances in which the intestinal wall may be weakened. A strong contraction or tonus wave from the unaffected bowel above the lesion may push fluid into the diseased portion and produce a perforation. It is suggested, therefore that subcutaneous injection of small doses of pitressin is indicated.

#### SUMMARY

The pressor, oxytocic and mixed principles of the posterior lobe of the pituitary gland, in the form of pitressin, pitocin and solution of posterior pituitary, were injected into man and dogs with balloons at various levels of their gastro-intestinal tract.

Nine subjects with ileal or colonic fistulas and one normal young woman who swallowed a stomach balloon were tested.

Of the nine patients with fistulas, eight responded to the drugs with increase in tonus and in the amplitude and height of the contractions. Violent contractions, tetanus, colic and defecation occurred in several of the subjects.

Caution appears indicated in the clinical use of pitressin, particularly when the intestinal wall is weakened.

Only one of three normal unanesthetized dogs manifested increased intestinal activity in response to pitressin. Apparently the temperament or disposition of the animal represents a contributing factor.

# LEIOMYOMA OF THE STOMACH

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It has been stated that a benign tumor of the stomach occurs so rarely that it may be regarded only as a clinical curiosity. More often it is taught that a tumor of this type is usually asymptomatic and that it is seen as a rule only incidentally at autopsy. A review of the literature, however, shows that, though decidedly infrequent, such a tumor may give rise to grave or persistent symptoms referable to the gastro-intestinal tract. The fact that a new growth of the stomach may be benign assumes a practical aspect in view of the importance of conserving such an organ as the stomach.

My interest in this subject was aroused recently by an unusual case in which severe gastric hemorrhage occurred. As the patient had suffered three attacks of hematemesis, two of which had been so severe as to reduce him to a state of shock, exploration of the gastric region seemed indicated. At operation a small leiomyoma of the stomach was removed, and the patient made an uneventful recovery. A complete report of the case is given here. In this instance the diagnosis of bleeding duodenal ulcer had been made. This error in diagnosis and the realization that the patient might have died at an early age from a remediable pathologic lesion had the surgeon not intervened caused me to make a careful study of the literature pertaining to leiomyoma of the stomach. It was hoped that definite correlation between the clinical and the pathologic picture might be revealed.

Excellent treatises are available on the general subject of benign gastric tumor, and complete monographs have been found dealing both with benign and with malignant tumor of smooth muscle origin occurring in the stomach. The collective papers presented information regarding the frequency of benign gastric tumor and of leiomyoma in particular. Eusterman and Sentry reported 27 cases of benign tumor of the stomach discovered at operation in a period during which 2,168 malignant gastric new growths were found at operation. This represents a proportion of 78 malignant tumors to 1 benign tumor; in other words, benign lesions constituted 1.3 per cent of all gastric tumors. Nadeau and McCarty reported a study of gastric tumors over a period of eight years, of which 1.2 per cent were benign. Lockwood stated

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that 5 per cent of all tumors of the stomach discovered at necropsy or removed at operation are benign. In the series of Eusterman and Sentry, 3 of the 27 benign tumors were leiomyomas. This constitutes 11.1 per cent of all benign gastric tumors. Farr and Glenn stated that myoma is the most important of the benign tumors in respect to frequency and the symptoms to which it gives rise. A study of the separate case reports was made to determine the symptomatology which may be attributed to leiomyoma of the stomach. To verify the statements made in the collective reports, the original articles to which they refer have been consulted.<sup>1</sup> In all, 56 cases have been found with sufficiently complete descriptions to establish the fact that the tumor in question was a benign lesion of smooth muscle origin. Twenty-three of these tumors were discovered at operation, and 33 are described in autopsy reports. The diagnosis of leiomyoma has been verified by consulting the microscopic descriptions of the tumors, except in some of the early cases in which the results of the microscopic examination are not recorded. In these, however, the gross pathologic descriptions were so complete that there is little doubt that each case was one of true leiomyoma of the stomach. Cases of fibromyoma, adenomyoma, other benign tumors or leiomyosarcoma of the stomach have been excluded from this report. With the addition of my 2 cases, there is, then, a total of 58 cases of leiomyoma of the stomach, in 25 of which the growth was found at operation and in 33 at autopsy. In 1 of the cases reported here the patient was observed and operated on by me; the other case was found in records of the New York Hospital. Twelve cases mentioned by F. Cohen and 5 by Nadeau and McCarty and 19 recorded by Geschickter in which no detailed accounts are given are not included in this paper.

#### CASES OF LEIOMYOMA DISCOVERED AT OPERATION

Twenty-five cases of gastric tumor are described in the literature in which the growth was clearly a leiomyoma and in which surgical treatment was instituted. My 2 cases are included in this number. In this group a study of the clinical data has been considered of great importance, since the patients presented symptoms of sufficient severity to justify surgical intervention. This is in contrast to the group of cases in which the growth was discovered at autopsy, in the reports of which symptoms often are not given or in which the constitutional changes occurring before death had so masked the clinical picture that the gastro-intestinal symptoms played no prominent rôle.

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1. Ninety-eight original papers have been consulted in this review of the literature. All cases variously reported as instances of leiomyoma in which the diagnosis was doubtful have been eliminated from this discussion.

The earliest case in this group is that of Rupprecht (1890). In his case the tumor, which weighed 251 Gm., was removed by gastric resection; the patient did not survive the operation.

The youngest patient operated on was a 9 year old boy, whose case was reported by Outland and Clendenning. A two stage gastric resection gave an excellent result. The oldest patient coming to operation was a man 78 years of age, whose case was reported by Yates. Partial gastrectomy was followed by recovery.

The age incidence in this group of cases was as follows:

Years	No. of Patients
0-10 .....	1
30-40 .....	4
40-50 .....	9
50-60 .....	3
60-70 .....	4
70-80 .....	1
Age not stated.....	3

In regard to sex, the occurrence was almost equal; in 22 cases in which the sex is given, 10 patients were males and 12 females.

Information is given in regard to race in only 5 cases; all the patients were Caucasians.

A detailed study of the symptoms, physical signs and gross pathologic picture in these 22 cases in which a leiomyoma of the stomach was found at operation indicates that they may be classified in the following distinct groups:

1. Cases of small leiomyoma which occurs in the region of the pylorus and manifests itself only by the symptoms of pyloric obstruction. In this group there are 8 cases, reported by Herhold, Samter, Peugniez and Jullien (2 cases), Outland and Clendenning, Eusterman and Sentry, Truesdell and me. In all these cases the symptoms were pain in the upper part of the abdomen and vomiting. The tumors are described as small (often referred to as the size of a nut) and located at or near the pylorus. The tumor in my case was 2.5 cm. in diameter. In only 2 cases was the tumor palpable on abdominal examination; in these cases it measured 8 by 6 cm. and 5 by 7 cm., respectively. Peugniez and Jullien described a tumor on the posterior wall, the proximity to the pylorus not being stated. The patient's symptoms were those produced by pyloric obstruction, and as the stomach was found to be dilated at operation the case has been included in this group.

2. Cases of large leiomyoma occurring in the fundus of the stomach and manifesting itself either by symptoms of partial gastric obstruction or by the presence of a palpable tumor. In this group there are 8 cases, reported by Rupprecht, von Erlach, Nicoladini, Goebel, Lowit,

Moura (2 cases) and Emmert. The locations of the tumors were given as follows: at the cardia, on the lesser curvature, on the anterior gastric wall (2 cases) and on the posterior surface of the middle one third of the stomach (2 cases). In two cases the site of the tumor was not indicated.

An idea of the size of the tumors in this group may be gained from the fact that 1 is said to have weighed 251 Gm., another 1,560 Gm. and a third 5,400 Gm. In 5 cases the sizes were variously recorded as "large as a child's head" (Goebel), "large as a man's head" (Lowit), 14 by 26 cm. (Nicoladini), 13 by 7 cm. (Moura) and 8 by 1 cm. (Moura).

In all patients except the last mentioned, an abdominal tumor was palpable. In 5 cases pain was the prominent symptom; consciousness of the tumor was recorded in 1 case, and symptoms were not listed in 1 case.

3. Cases of small leiomyoma at a distance from the pylorus and manifesting itself by severe gastro-intestinal hemorrhage. In this group there are 4 cases, reported by Thompson, Eusterman and Sentry, Eusterman and Balfour and me. The tumors were 2 cm. in diameter, 0.5 by 2 cm. in diameter, 3.5 by 5.5 by 4 cm. and 6 by 4 cm. in size. The weights of the tumors are not recorded. All were distinctly encapsulated lesions. In my case there were definite folds in the mucosa over the tumor, giving the suggestion of the formation of crypts; at one point there was a minute ulceration 3 mm. in diameter (fig. 1). The same type of mucosal crypt formation was seen in Thompson's case, but no ulceration was evident. A photograph of Thompson's specimen is shown in figure 2. He referred to the tumor as a fibromyoma, but the microscopic sections indicate that it was a tumor chiefly of muscle cell origin. The gross pathologic picture so closely resembled that in 1 of my cases that it has been included in the group. All 4 of these patients were subjected to operation because of severe hematemesis or recurring melena. My patient had grave hematemesis, on two occasions so severe as to cause profound shock. The patient of Eusterman and Sentry had symptoms of recurring melena and hematemesis and exhibited marked anemia. The patients of Thompson and of Eusterman and Balfour had recurrent melena and massive gastric hemorrhage.

These patients were 41, 42, 45 and 54 years of age, respectively.

Five cases in which a gastric leiomyoma was discovered at operation fail to fit into any of the foregoing groups. In 3 of the 5 cases neither the symptoms nor the position of the tumor was given. In Eusterman and Sentry's case the tumor was said to have been near the pylorus, and the symptomatology was given as a "duodenal ulcer syndrome."



For lack of more detailed information, this case could not be classified. Yates reported a case in which a small tumor was found on the posterior wall of the stomach. The patient's chief symptom was epigastric distress after meals. A cholecystectomy was done at the time the tumor was removed, and it is possible that the epigastric distress was due to the pathologic process in the gallbladder and that the tumor was asymptomatic. More will be said about the small asymptomatic leiomyoma in the discussion of cases in which the growth was discovered at autopsy.

#### OPERATIVE TREATMENT; IMMEDIATE AND LATE RESULTS

The operative treatment is recorded in 19 of the 25 cases as follows:

Operation	No. of Cases
Partial gastric resection .....	4
Partial gastric resection, pyloroplasty .....	2
Partial gastric resection, cholecystectomy .....	1
Partial gastric resection, gastro-enterostomy .....	1
Pylorectomy .....	1
Pylorectomy, gastro-enterostomy.....	1
Billroth operation (II).....	1
Polya-Mayo's operation.....	1
Two stage gastric resection.....	1
Annular gastrectomy.....	1
Median gastric resection.....	1
Removal of tumor.....	3
Exploratory laparotomy, stomach torn, wound packed...	1

The patients on whom annular gastrectomy and exploratory laparotomy was performed died after operation. There was also one fatality in the 3 cases in which the tumor was removed. The patient on whom partial resection was done failed to recover.

In only 19 of the 25 cases was the result of operation stated; in 15, or 78.9 per cent, of these recovery followed operation, and in 4, or 21.1 per cent, the patients died. One of the 4 patients died of embolus fifteen days after operation; the second died of peritonitis on the eighth postoperative day; the third died ten months after operation, of complications brought about by complete separation of the wound, and the fourth died a few days after removal of the tumor, the cause of death not being stated. It is to be remembered in evaluating the mortality that of 4 deaths, 2 (Rupprecht and Nicoladini) occurred before the close of the nineteenth century.

Eight patients recovered from operation, but no follow-up report is given. Seven others recovered and were reported as well two months, six months, six months, seven months, and one year, one and one-half year and three years, respectively, after operation.

The 25 cases in which a leiomyoma of the stomach was discovered at operation were described by Rupprecht, von Erlach, Nicoladini, Herhold, Samter, Yates, Goebel, Thompson, Bland-Sutton (2 cases), Peugniez and Jullien (2 cases), Lowit, Outland and Clendenning, Eusterman and Sentry (3 cases), Moura (2 cases), Ungar, Truesdell, Eusterman and Balfour, Emmert and me (2 cases).

The reports of my 2 cases of leiomyoma of the stomach follow:

CASE 1.—F. S., a white man aged 41, was admitted to the surgical service of the New York Hospital in a state of profound shock after sudden hematemesis. The immediate therapy was directed toward the replacement of blood. Subsequently the patient passed a number of copious tarry stools, but his condition gradually improved. After three days of fasting he was given a Sippy diet; this was followed by sudden hematemesis, with the loss of approximately 1 pint (473 cc.) of bright red blood. The patient again went into shock and was desperately ill for four days. He slowly recovered from the profound anemia.

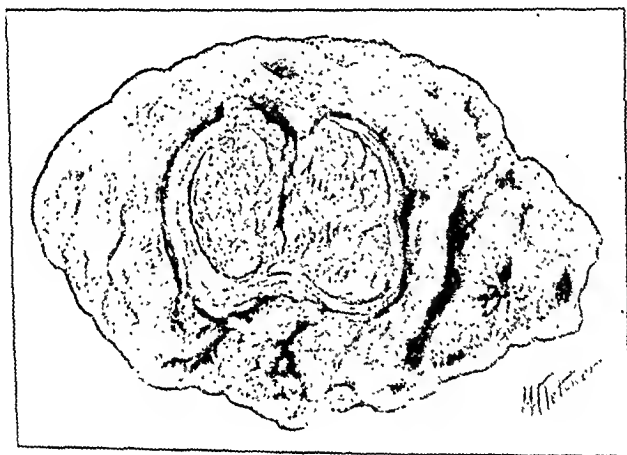


Fig. 1 (case 1).—Leiomyoma of the stomach. Note the thick capsule of the tumor.

The patient stated that for nine years he had had gastric pain after eating, which was usually relieved by taking sodium bicarbonate or food. At another institution he had been placed on a Sippy diet with relief of his symptoms. Three years before admission to the New York Hospital he had an attack which suggested gastric hemorrhage, and serial roentgenograms of the gastro-intestinal tract made by Dr. Arthur L. Holland at this time showed a defect on the lesser curvature, which was thought to represent a gastric ulcer. After dietary therapy this defect disappeared.

The family history was irrelevant save for the fact that the patient's mother died of carcinoma of the stomach.

Physical examination on admission gave negative results, except for the evidences of shock. The patient was a fairly well developed and well nourished man. The pupils reacted normally to light and in accommodation, and the fundi were normal. The blood pressure was 120 systolic and 80 diastolic. The heart and lungs were normal. There was no abdominal tenderness. The liver and spleen were not palpable. The extremities showed no abnormalities.

As soon as the gastric bleeding ceased, serial roentgenograms of the gastrointestinal tract were made on two occasions. At neither time was anything abnormal seen in the fluoroscopic examination of the stomach and duodenum. A gastric analysis was not done for fear of starting another violent hemorrhage. The Wassermann reaction of the blood was negative.

An exploratory operation revealed a small tumor, measuring 2 by 2 cm., in the wall of the stomach. It was roughly oval and was located on the lesser curvature of the stomach 6 cm. from the pylorus. The gastric serosa overlying the tumor mass appeared to be normal, and when the stomach was opened the mucosa was seen to be intact over it. The tumor presented a hard, encapsulated mass in the gastric wall, apparently not attached to the mucosa or the serosa. A diamond-shaped section of the stomach was excised which included the lesion and a wide margin of normal gastric wall. A posterior gastro-enterostomy was done.

A section of the tumor is shown in figure 1. Gross examination revealed two distinct crypts of the mucosa directly overlying the tumor. A minute ulceration

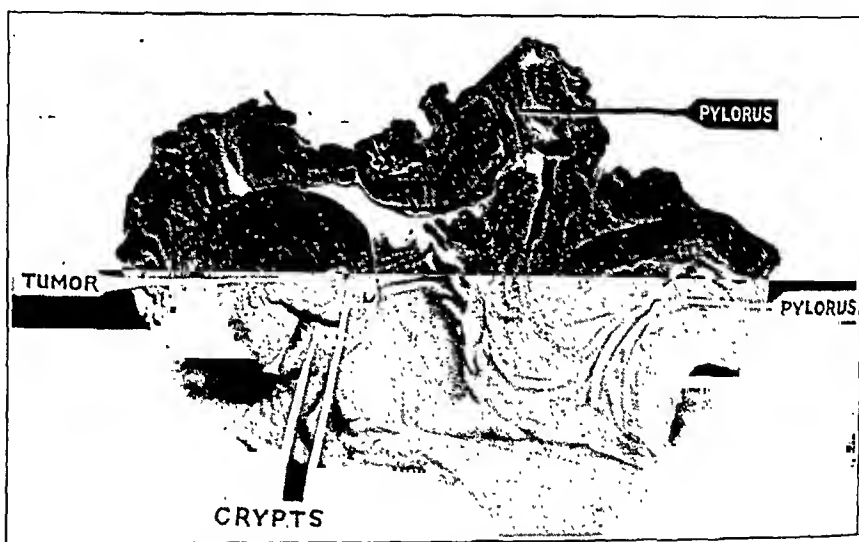


Fig. 2.—Photograph of the tumor and a portion of the stomach in Thompson's case. The report of Morgan's case shows a photograph of a tumor which has a striking resemblance to this one (Thompson, J. E.: *Tr. South. S. Gynec. A.* 21:17, 1909).

of the mucosa, 3 mm. in diameter, also was evident. The cut surface of the specimen was dull grayish white. Dr. N. Chandler Foot described the gross and microscopic appearance of the tumor as follows:

The tumor was definitely circumscribed by a tough brawny white capsule about 4 mm. in thickness, from which it bulged on section. The whole growth was embedded in the muscular portion of the gastric wall and was covered on one aspect by mucosa and on the other by serosa. At one point in the former, over the convexity of the tumor, there was a small ulceration, about 3 mm. in diameter, with a congested base and a slightly necrotic raised rim. The tumor itself was about 3 cm. in diameter and was set off from the capsule both by its pinker color and by its softer and more meaty consistence. It bulged about the cut surface, was finely lobulated and cut without noticeable resistance; there was no gritty sensation as the knife passed through it.

Microscopic sections showed the tumor to be of unmistakable smooth muscle origin; the cells were poorly matured leiomyoblasts of a type intermediate between the primitive cell seen in the leiomyosarcoma and the more adult form encountered in the leiomyoma. The large ovoid and somewhat hyperchromatic nuclei occupied the middle of the cells and were surrounded by feathery, poorly consolidated masses of smooth muscle. This is well shown in the photomicrograph. Mitotic figures were not found after considerable searching, and there was no marked invasion of the capsule by the growth. For this reason the tumor was classified as a nonmalignant leiomyoma with a very cellular and somewhat anaplastic make-up.

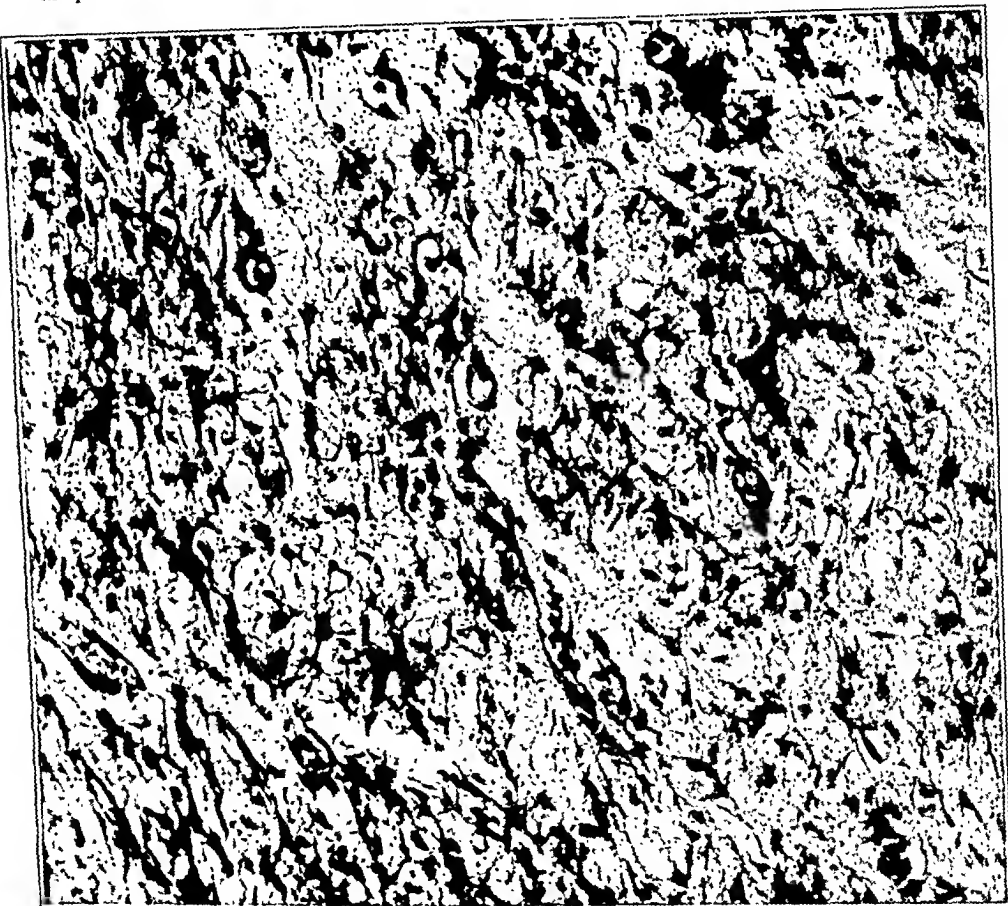


Fig. 3 (case 1).—Low power photomicrograph of a section of the leiomyoma shown in figure 1. Note the poorly matured leiomyoblasts.

The diagnosis was leiomyoma of the gastric wall.

Photomicrographs are shown in figures 3 and 4. From a clinical point of view the lesion has been considered a benign tumor of the stomach, as it was well encapsulated and without evidence of infiltration and as there was no regional glandular enlargement. The liver appeared normal at operation, and save for a few adhesions around the duodenum the abdomen presented no other abnormalities.

The patient had an uneventful convalescence and was reported to be well nineteen months after operation.

CASE 2.<sup>2</sup>—An Italian cook, aged 44, was admitted to the New York Hospital with the complaint of epigastric pain of five years' duration. This pain occurred characteristically from fifteen to thirty minutes after meals and lasted from forty-five minutes to one hour. It was relieved by taking sodium bicarbonate or by assuming a recumbent position. Two months before admission the patient vomited frequently after eating. Anorexia developed, and there was a loss of weight of 20 pounds (9.1 Kg.) in the six weeks prior to the patient's admission to the hospital. Dietary measures failed to give relief from the symptoms. There was no melena and no hematemesis.

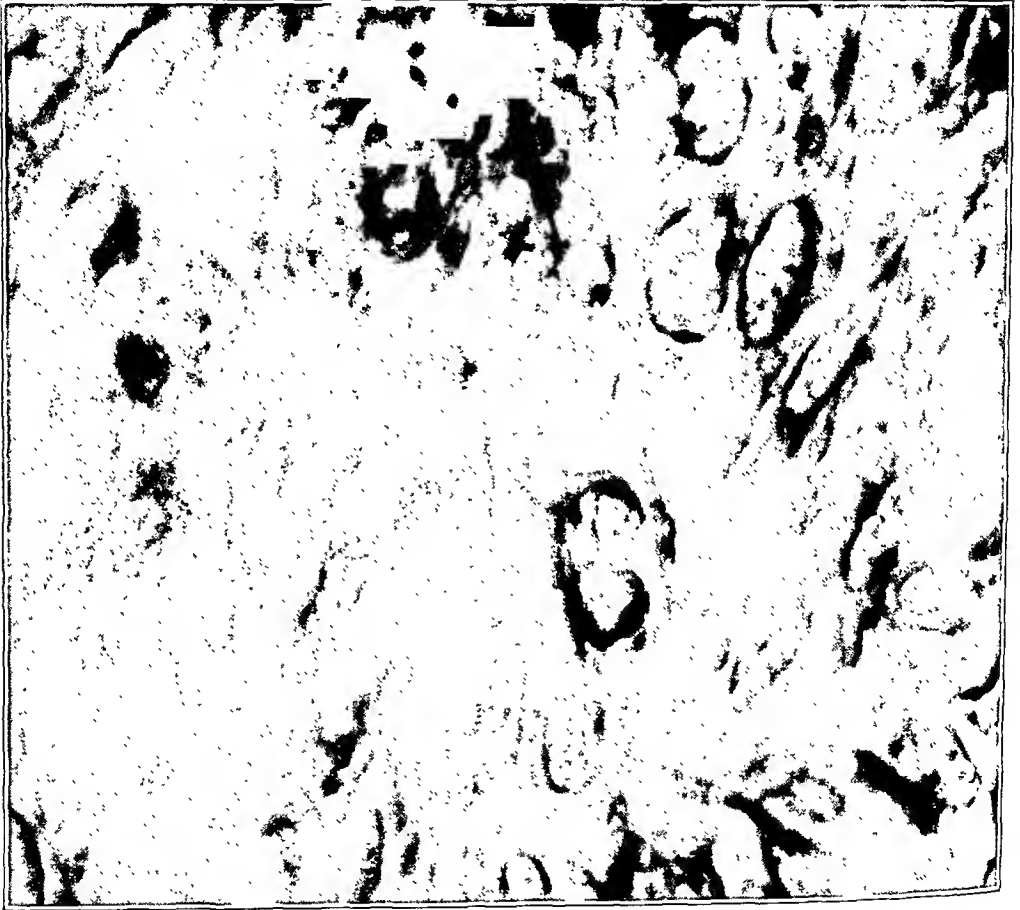


Fig. 4 (case 1).—High power photomicrograph of a section of the leiomyoma shown in figure 1. Note the large, ovoid and somewhat hyperchromatic nuclei surrounded by poorly consolidated muscle substance.

The family history was irrelevant, and the past history was not remarkable. At the age of 9 years the patient had an operation for the removal of a right inguinal gland.

He had occasional nocturia, but urinalysis gave negative results.

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2. Dr. Charles L. Gibson kindly gave me permission to include this case report.

Physical examination showed that the man evidently had lost some weight; he appeared chronically ill. The only significant finding was an elongated epigastric mass which was somewhat tender on palpation and which could not be sufficiently well outlined for measurement. The blood pressure was 120 systolic and 80 diastolic.

The laboratory tests resulted in the following findings: red blood cells, 4,500,000; white blood cells, 11,600, and hemoglobin, 90 per cent. The differential count showed 72 per cent polymorphonuclears, 5 per cent monocytes and 1 per cent eosinophils. The Wassermann reaction of the blood was negative, and the stool showed no blood. Analysis of the gastric contents after an Ewald test meal showed 27.6 units of free hydrochloric and 59.8 units of total acid. The blood urea content was 18 mg. per hundred cubic centimeters, and the icteric index, 7.

A roentgenogram of the gastro-intestinal tract showed a persistent filling defect in the antrum involving both curvatures. Six hours after a barium sulfate meal there was no sign of gastric retention.

The operation, performed by Dr. Gibson, revealed a movable tumor the size of "a silver dollar" in the prepyloric region. It was described as a hard irregular grayish tumor. There was no glandular enlargement. A Polya-Mayo resection of the lower one third of the stomach was carried out.

Dr. Lawrence Smith, who made the pathologic examination of the tumor, described it as follows: The specimen consisted of the terminal 3 inches (7.6 cm.) of the stomach and approximately 1 inch (2.5 cm.) of duodenum. There was definite thickening of the pyloric ring, which was most marked on the side of the lesser curvature. Here a disklike mass, approximately 1.5 cm. in diameter, could be felt beneath the mucosa but adherent to it centrally. Its lower margins appeared to be free; centrally it merged with a small sausage-shaped semifluctuant tumor, 2.5 by 1 cm. in diameter. On section it appeared to be composed of irregularly arranged strands of hypertrophied muscle tissue. The deeper discoid mass was extremely dense in consistence and obviously fibrosed. The mucosa showed no erosions, and its adherence to the mass was probably secondary to inflammatory changes.

A frozen section of the larger mass confirmed the impression given by the gross specimen that it was a simple benign tumor of smooth muscle origin. The disklike tumor was composed of dense connective tissue which showed some myxomatous degeneration. There was no definite evidence of malignancy after careful study. There were many large pale-staining clear cells reminiscent of signet ring cells. They, however, appeared to resolve themselves into fat cells or large mononuclear phagocytes laden with lipoids. A photomicrograph of a section is shown in figure 5. The general reaction was characterized by fibrosis and chronic inflammatory cellular infiltration. Superficial ulceration and repair were noted in small areas of the mucosa.

The diagnosis was gastric ulcer (healed) and leiomyoma of the wall of the stomach.

The patient made an uneventful recovery and was discharged on the twentieth day after operation. Up to the present time attempts to obtain information regarding the late results in this case have been unsuccessful.

#### CASES OF LEIOMYOMA DISCOVERED AT AUTOPSY

The records of the 33 cases in which a leiomyoma of the stomach was discovered at autopsy have been studied in regard to the rôle played by the tumor in causing death. In only 21 of these cases was the cause of death recorded.

In 6 cases it was clearly stated that death was due to massive gastric hemorrhage. These are the cases of Niemeyer, Kemke, Miodowski, Fischer-Loewenstein, Morgan and Farr and Glenn. In only 4 cases was the size of the tumor mentioned; in 1 it was 4.5 by 5 cm., in 1  $1\frac{1}{2}$  by 2 inches (3.7 by 5 cm.), in 1 the "size of an apple" and in 1 the "size of an egg." One tumor was located at the lesser curvature, 1 in the middle of the greater curvature, 1 at the fundus and 1 on the anterior gastric wall. The ages of the patients ranged from 49 to 70

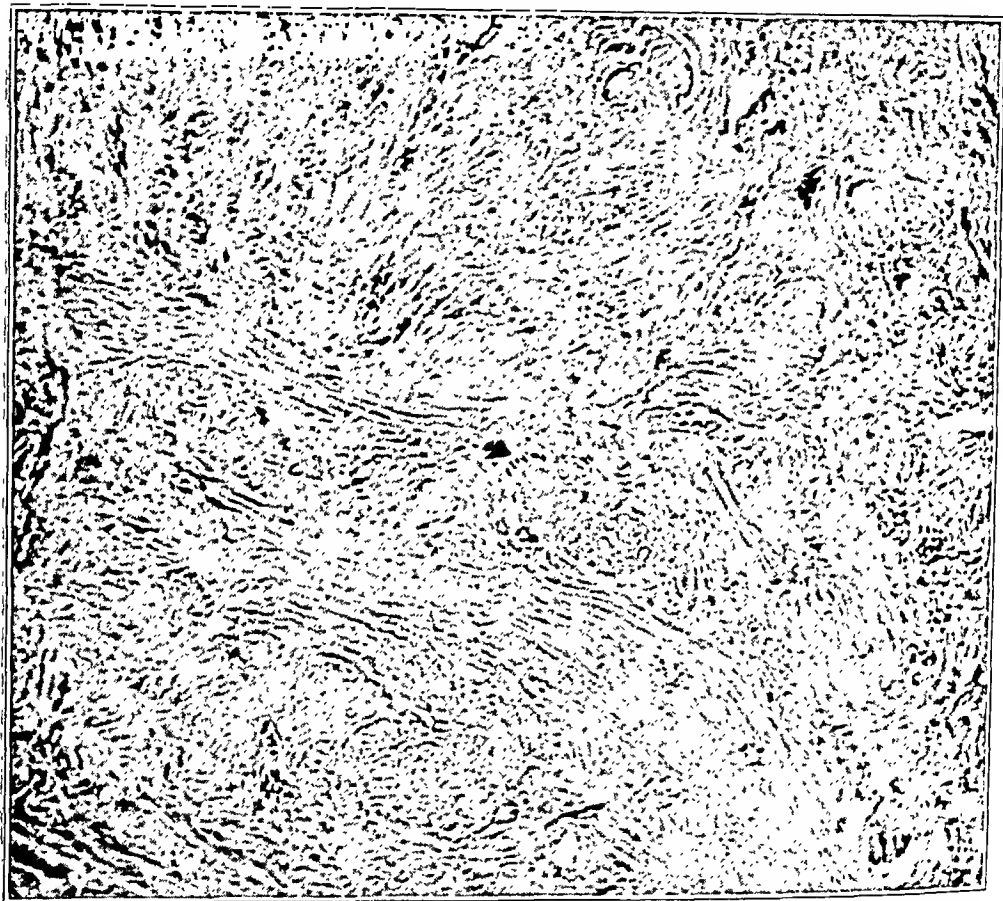


Fig. 5 (case 2).—Low power photomicrograph of a section of a leiomyoma showing the smooth muscle cells.

years. It is significant that in the cases in which the size and location are given, the tumor was described as small and not near the pylorus. These cases aline themselves with those of the group in which the tumor was discovered at operation performed for gastric hemorrhage.

In 13 cases it is clearly stated that the patient died of a cause unrelated to the gastric tumor. These are the cases of Vogel, Virchow, Jean, Cutler, F. Cohen (2 cases), Caminiti, and Mouriquand and

Gardère, Lotsch, Hake (3 cases) and Max. These cases, then, are instances of a type of asymptomatic leiomyoma of the stomach which is discovered incidentally at postmortem examination. In all of these cases the tumor was small and variously described as the size of a nut, pea, cherry, etc. The largest lesion occurred in one of Hake's cases, in which a tumor 8.7 by 5 cm. was found near the cardia. Its location in the stomach may have accounted for the fact that it did not produce any symptoms. The type of case in this group is undoubtedly responsible for the common teaching that a benign tumor of the stomach is of no clinical significance and should be regarded only as a matter of curiosity at autopsy.

One patient (Battay) is said to have died as a result of toxic absorption from the tumor, an hour glass, pedunculated mass, which had enlarged both under the mucosa and under the serosa of the stomach. Several sinuses in its surface discharged foul pus.

In 1 other case, the last of the 20 in which the cause of death was stated, the tumor may have been a contributory lethal factor. In this case (Ferguson) the patient exhibited marked anemia, pellagra and bilateral pleural effusion. The cause of death is not clearly stated in the report, but since the tumor was described as of "unusual size" and at the cardia, it is possible that it was responsible for the chain of clinical events which led to death.

In none of the cases in which the growth was found at autopsy has pyloric obstruction due to leiomyoma been given as the cause of death. The reason for this may be that the symptoms of pyloric obstruction, if at all severe, demand surgical intervention, and the patients undoubtedly have been subjected to operation.

The age of the patient at the time of death was recorded in 19 of the 33 cases as follows:

Age	No. of Cases
10-20 .....	1
20-30 .....	1
30-40 .....	0
40-50 .....	4
50-60 .....	5
60-70 .....	4
70-80 .....	1
80-90 .....	3

Of the 21 cases in which the sex was recorded, 9 were in males and 12 in females. The race was mentioned in only 3 cases; all the patients were Caucasians.

The position of the gastric tumor is reported in only 19 cases. In none of these was it obstructing the pylorus, but in 3 (Jean, F. Cohen and Caminiti) the position of the tumor was recorded as near or



"around" the pylorus. The cause of death in these 3 cases was: (1) lobar pneumonia, (2) death following operation for myoma of the uterus and (3) pulmonary tuberculosis. The location of the tumor in the stomach was as follows in the 19 cases in which it was noted:

Location	No. of Cases
Posterior wall.....	1
Lesser curvature near cardia.....	4
Anterior wall near pylorus.....	2
Lesser curvature.....	1
Greater curvature.....	2
Fundus .....	2
Around the pylorus.....	1
Near the pylorus.....	1
Middle of the greater curvature.....	1
Posterior surface.....	1
Posterior wall near the cardia.....	1
Cardia .....	1
Between the greater and the lesser curvature.....	1

In only 24 of the 33 cases was reference made to the size of the tumor. The largest was 9 by 8 cm. Many were listed as the "size of a nut," "bean," etc. In 1 case there were 4 pea-sized tumors in the stomach (Laboulbène) and in another, multiple leiomyomas, 60 in all, of the gastro-intestinal tract, only 1 of which was in the stomach (Nazzarri).

The weight of the leiomyoma discovered at autopsy was given in only 2 cases; in Morgagni's case the tumor weighed 1 pound (0.5 Kg.); this was the first leiomyoma of the stomach to be reported (1762). In Perls-Neelsen's case the tumor weighed 6 Kg. This tumor has often been referred to (Thompson) as the heaviest leiomyoma of the stomach ever reported, but the weight has been mentioned in so few instances that it is impossible to accord special significance to the tumor reported by Perls-Neelsen.

In only 6 of the 33 cases of leiomyoma of the stomach found at autopsy were symptoms recorded. In these 6 cases death was due to gastric bleeding, and the symptoms were tarry stools and massive hemorrhage from the stomach. The 33 cases in which leiomyoma of the stomach was discovered at autopsy were the cases of Morgagni, Foerster, Vogel, Virchow, Jean, Cutler, Laboulbène, Perls-Neelsen, Niemeyer, Kemke, Steiner (3 cases), F. Cohen (3 cases), Nazzarri, Borst, H. Cohn, Caminiti, Miodowski, Fischer-Loewenstein, Max, Battey, Mouriquand and Gardère, Anitschkow, Lotsch, Hake (3 cases), Ferguson, Farr and Glenn and Morgan.

## COMMENT

A review of the literature on benign tumors of the stomach of muscle cell origin reveals the following facts in regard to the incidence and pathologic characteristics of gastric leiomyomas:

The distribution in regard to sex is practically equal.

The youngest patient in whom such a tumor is known to have occurred was 9 years old.

Such a tumor may occur not only in the stomach but also in the esophagus and intestines and may be multiple in all of these organs.

The tumor may be found in any portion of the stomach.

Gross pathologic descriptions, in general, establish the fact that this type of tumor is encapsulated and nodular and that on section the surface bulges. The tumor may be external and project into the peritoneal cavity, in which case the serosa of the stomach is freely movable over the capsule; it may be internal and invade the lumen of the stomach, in which case the mucosa is freely movable over its capsule (Steiner). Definite mucosal folds or crypts have been described in the mucosa of the stomach over the surface of the tumor, and in a few cases small ulcerations of the mucosa have been reported. The weights of the tumors vary exceedingly; the heaviest tumor weighed 6 Kg. The variation in size is equally marked. The smallest tumors are described as "pea-sized," while the largest have been reported to be "as large as a man's head."

## SUMMARY

A careful study of the literature on benign tumor of the stomach has been made for the purpose of collecting all reported cases of true gastric leiomyoma and of correlating, as far as possible, the clinical and pathologic pictures. Reports of 56 cases were found in the literature, and 2 new cases are added. Twenty-five of these were found at operation and 33 at autopsy.

An analysis of the clinical and pathologic picture in the 56 cases suggests their classification under four headings, as instances of:

(a) Small leiomyoma which occurs near the pylorus and produces pyloric obstruction.

(b) Large leiomyoma which occurs in the fundus of the stomach and causes partial gastric obstruction.

(c) Small leiomyoma located at a distance from the pylorus which gives rise to severe gastric hemorrhage.

(d) Small leiomyoma which is asymptomatic.

Two new cases are described in detail; 1 in which gastric hemorrhage made operation imperative and 1 in which a small tumor at the pylorus caused obstruction, which was relieved by resection of the tumor.

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# HYPOPARATHYROIDISM FOLLOWING OPERATION FOR HYPERPARATHYROIDISM DUE TO ADENOMA TOLERANCE FOR PARATHYROID EXTRACT

ROY D. McCLURE, M.D.

DETROIT

Death following the surgical removal of a parathyroid tumor or following the accidental removal of the parathyroid glands in the course of a thyroidectomy is sufficiently rare to justify the report of such a case and a discussion of the probable causes of death following removal of a parathyroid adenoma when the use of calcium salts, vitamin D and parathyroid extract and transplantation of parathyroid tissue failed.

Aub<sup>1</sup> was the first to report and analyze the failure of parathyroid extract to control parathyroid tetany after thyroidectomy.

The patient at the age of 18 underwent a subtotal thyroidectomy twice within the year 1917 for symptoms of exophthalmic goiter of three years' duration. Two months after the second operation, attacks of choking and carpopedal spasm with edema of the face and extremities developed. Two years after the second thyroidectomy, operation was necessary for bilateral cataract. Parathyroid extract was first given in 1926, nine years after thyroidectomy. At that time the patient was still having attacks of tetany; the basal metabolic rate was minus 18 per cent (before thyroidectomy it had been plus 45 per cent); the serum calcium content was 4.3 mg. per hundred cubic centimeters, and the inorganic phosphorus content, 5.6 mg. Fifteen units of parathyroid extract given daily for a week, together with thyroid extract, raised the serum calcium content to 6 mg. and the basal metabolic rate to plus 11 per cent, the blood phosphorus content falling to 4.2 mg. As a result, the attacks of tetany ceased. The administration of parathyroid

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From the Henry Ford Hospital.

Dr. Arthur B. McGraw and Dr. Don C. Robertson have helped in the preparation of this paper.

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extract, however, had to be continued and gradually increased in order to prove effective. Finally, after some months, doses of 100 units had no effect. The eventual results of this failure were disastrous, for the persisting low serum calcium content was accompanied by severe attacks of tetany, associated with bronchial and pharyngeal spasm and unconsciousness, and in such an attack the patient died.

Aub<sup>1c</sup> interpreted this phenomenon as an "immunity" to parathyroid extract. When such an immunity appears, even large doses of parathyroid extract exert no influence on the calcium or phosphorus content of the blood. He stated that this loss of potency has lasted in one case for a year and is dependent on resistance to the preparation and not on drainage of the storehouse of calcium, for an increase in the excretion of calcium followed the administration of ammonium chloride after parathyroid extract had proved ineffective.

The first fatal case of hypoparathyroidism following parathyroidectomy in this country was reported by Wilder, Camp, Robertson and Adams.<sup>2</sup>

The patient, a woman aged 48, had had some alleged rheumatic symptoms consisting of pain in the knees and the lower part of the back radiating down the thighs for three years. The severity of the pain confined her to bed. In spite of roentgen evidence of osseous rarefaction, a diagnosis of hyperparathyroidism was rejected on account of a normal content of serum calcium and serum phosphorus.

Therapy with viosterol and calcium lactate caused a remission of symptoms for nearly two years, when the symptoms again became serious and further roentgenograms showed increased rarefaction of the pelvic bones, with features clearly characteristic of fibrous osteitis. The calcium and the phosphorus content of the serum were again within normal limits, but the phosphatase content of the blood was abnormally elevated, and there was a slightly negative calcium and a positive phosphorus balance when the patient was on a diet containing only 0.159 Gm. of calcium. Surgical exploration at this time by Dr. F. W. Rankin revealed a parathyroid tumor 2 by 1.5 by 1 cm. in the groove between the trachea and the esophagus. On section, the structure was that of an adenoma.

After operation the serum calcium content rapidly fell to 5.5 mg. per hundred cubic centimeters. The patient manifested symptoms of tetany, which were not relieved by large daily doses of dibasic calcium phosphate ( $\text{CaHPO}_4$ ). The tetany yielded to an injection of 15 units of parathyroid extract and was subsequently prevented by the daily administration of 20 Gm. of calcium lactate. The pain completely disappeared, and for a short time there was a positive calcium balance. At the end of the third week, however, a negative calcium balance again set in, accompanied by nausea, vomiting, meteorism, abdominal cramps and diarrhea. The calcium and the phosphorus content of the serum fell below normal levels and did not yield to injections of parathyroid extract. Nutritional edema developed, and the patient died one and one-half months after operation.

2. Wilder, R. M.; Camp, J. D.; Robertson, H. E., and Adams, M.: Fatal Case of Hyperparathyroidism, with Report of Necropsy, *Proc. Staff Meet., Mayo Clin.* 7:597-606 (Oct. 19) 1932.

The following case has many features similar to the one just reported, even to the resistance of the patient to parathyroid extract, for which my colleagues and I have attempted to find an explanation.

E. D., a white woman aged 51, married, was admitted to the Henry Ford Hospital on March 1, 1934. Her chief complaint was soreness of the left leg (at the site of fracture thirty-one months before) and a hard, painless swelling below the right elbow. She had typhoid at the age of 17, arthritis in all the joints for the past seven years, pneumonia and pleurisy five years before admission, occasional nocturnal dyspnea and frequency and urgency of urination.

The present illness began six years before admission, when a fall on the right arm resulted in a hard painless enlargement just below the right elbow, which had persisted. Two and one-half years before admission the patient slipped on



Fig. 1.—Roentgenogram of the left femur, showing a fracture in the upper third of the shaft. Note the osteoporosis and thinning of the cortex. The picture was taken at the Providence Hospital on Sept. 2, 1931.

a waxed floor and fractured the shaft of the left femur (fig. 1). She was hospitalized elsewhere for six weeks and then returned home after a cast was applied. When allowed on crutches three months after the accident, she noted soreness and tenderness at the site of the fracture, which never disappeared. She has never been able to bear much weight on the left leg and has noticed local heat at the site of injury from time to time.

Physical examination revealed the following: temperature, 98.2 F.; pulse rate, 76; respiratory rate, 18, and weight, 127 pounds (57.6 Kg.). The patient appeared tired and worn. There was some graying of the hair, but it was normal in texture and distribution. The thyroid gland was not enlarged and felt smooth. A marked pulsation, synchronous with the heart beat, was palpable in the supra-sternal notch and above the right clavicle. The heart sounds were a little distant

but regular, and no murmurs were audible. The blood-pressure was 140 systolic and 84 diastolic. There was slight tenderness over the descending colon. Some leukoplakia of the vulva was noted. There was roughly 2.5 cm. of shortening of the left lower extremity, with a painful tender fusiform enlargement near the midportion of the femur. A hard bony fusiform enlargement of the right ulna just below the elbow was noted. There was a hallux valgus deformity on the right.

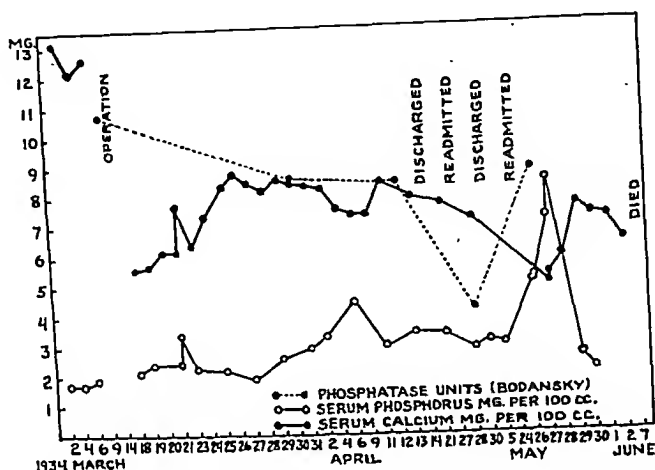


Fig. 2.—Curves showing the values for calcium, phosphorus and phosphatase.



Fig. 3.—Electrocardiogram made before resection of the parathyroid adenoma. The RT time was 0.2 second (normal RT time, 0.26 to 0.28 second). The record was taken on March 5, 1934.

One determination of the basal metabolic rate was minus 3 per cent. Urinalysis gave negative results. The hemoglobin content was 83 per cent, or 13.2 Gm., and the leukocytes numbered 7,300. The Wassermann test was negative. The calcium content of the blood was 12.2 mg. and the phosphorus content, 1.8 mg. per hundred



cubic centimeters (fig. 2). There was 10.72 units (Bodansky<sup>3</sup>) of phosphatase. The calcium balance averaged plus 0.31 Gm. per day for one three day period of study.

The electrocardiogram showed a diphasic T wave in leads I and II, slight left ventricular preponderance, occasional ventricular extrasystoles and sinus tachycardia and indicated some degree of myocardial degeneration. There was a slight shortening of the RT time to around 0.2 second (fig. 3). This corresponds with the electrocardiographic changes previously observed by Spalding<sup>4</sup> in cases of hyperparathyroidism.

The roentgenograms (fig. 4) of the skull, left femur, pelvis, left humerus, right forearm and mandible showed osteoporosis varying from a moderate to a marked amount. Cystlike areas were present in the mandible, the right ulna and the left femur. The latter also showed an old fracture at the junction of the



Fig. 4.—*A*, roentgenogram of the left femur before operation, taken on March 1, 1934, at the time of the patient's admission. *B*, roentgenogram of the mandible before operation, taken on March 6, 1934. *C*, roentgenogram of the right radius and ulna before operation, taken on March 5, 1934. Several small cystlike areas were also present in the lower ends of these bones.

middle and the upper third, where an extensive cystlike process was present. Roentgenograms (fig. 1) of the site of the fracture received three years before revealed a marked amount of osteoporosis and some thinning of the cortex in addition to the displaced fragments. The foregoing changes were felt to be quite characteristic of osteitis fibrosa cystica secondary to hyperparathyroidism.

3. All phosphatase determinations in this report are expressed in terms of Bodansky units.

4. Spalding, E. D., quoted by Ballin, M.: Parathyroidism, *Ann. Surg.* 96: 649-665, 1932.

Resection of the parathyroid adenoma and partial thyroidectomy were performed on March 14.

The thyroid gland was well exposed on each side of the neck, through the conventional collar incision with retraction of the ribbon muscles. The gland was slightly enlarged, and there was a firm nodule 2 cm. in diameter lying within the lower pole of the right lobe (fig. 5). Careful search was made for the parathyroid glands in the usual position, but none was identified. The right lobe of the thyroid was removed in order to make sure, if possible, that the parathyroid glands were removed, as it was thought that the tumor completely embedded in the thyroid was not composed of parathyroid tissue. Immediately on removal of the thyroid tissue it was sectioned by the pathologist. (See his note.) Search of the left lobe of the thyroid failed to show any parathyroid adenoma, and a portion

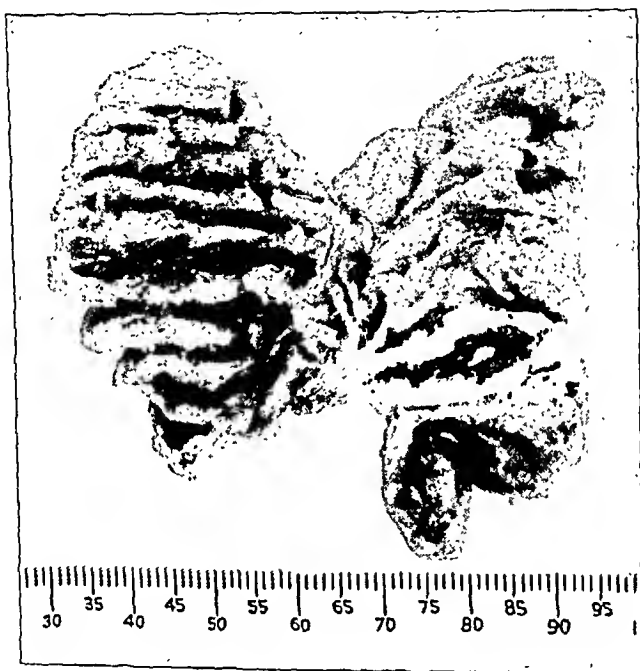


Fig. 5.—Photograph of a dissected gland, showing parathyroid adenoma embedded in thyroid tissue of the right lower pole. The adenoma measured 2 cm. in diameter and presented a thick fibrous capsule and a cystic central portion containing brown fluid.

of the lower pole of this lobe was removed. Careful search, however, of the tissue removed failed to show any parathyroid tissue present, excepting the tumor enclosed in the lower pole of the right lobe.

The following is the pathologic report by Dr. Frank Hartman: Section through the lower pole of the right lobe revealed a cystic adenoma (fig. 5) 2 cm. in diameter. The outer portions of the adenoma were yellowish brown and solid. From this tissue finger-like processes extended into the cyst, which was filled with bloody fluid. The tissue was soft and friable. In addition to the tissues mentioned there were a number of small bits of tissue which had been removed during the course of examination from the surface of the thyroid gland and

examined by frozen sections. These pieces of tissue were shown histologically to be isolated lobules of thyroid tissue, lymphoid tissue and fatty tissue. Frozen sections unfortunately were not made of the adenoma, and in the gross specimen this was interpreted as a degenerating adenoma of the thyroid gland largely because of its location in the substance of the gland.

Microscopic examination of sections from different portions of thyroid tissue showed the acini of the gland to be rather small and lined by flattened epithelium.

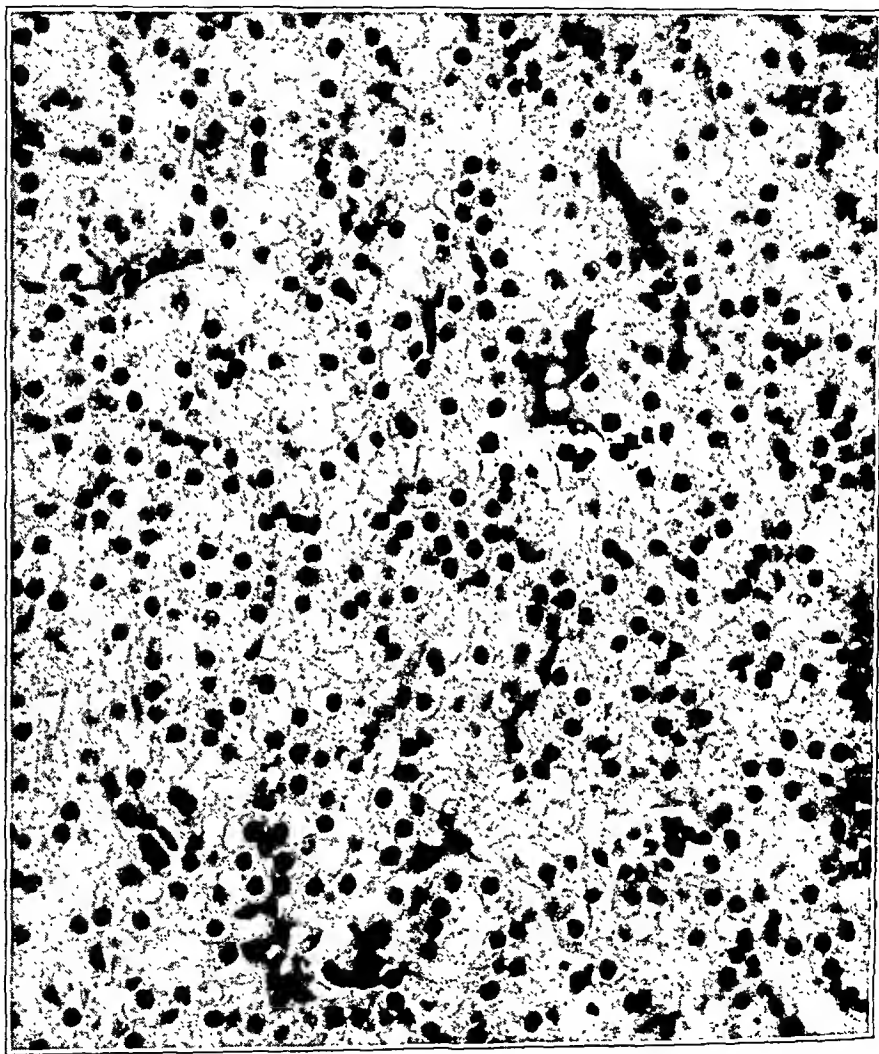


Fig. 6.—Medium power photomicrograph showing a group of oxyphilic cells at the periphery of the tumor. Some cells have a larger clear space about the nucleus.

The lumens were filled with dense pink-staining colloid material. Here and there collections of small round cells were seen.

Sections from the tumor (figs. 6 and 7) in the lower pole of the right lobe of the thyroid gland showed the same, surrounded by a rather dense fibrous capsule.

Within the capsule there was a rather thick layer of large polyhedral cells; which for the most part had pink-staining cytoplasm: The nuclei were relatively large and hyperchromatic. There was a clear space about the nucleus in most of the cells, even in this area. As the central portions of the tumor were approached, the vacuolation was more pronounced, and in some areas the cytoplasm was almost entirely clear. In the latter areas the nucleus tended

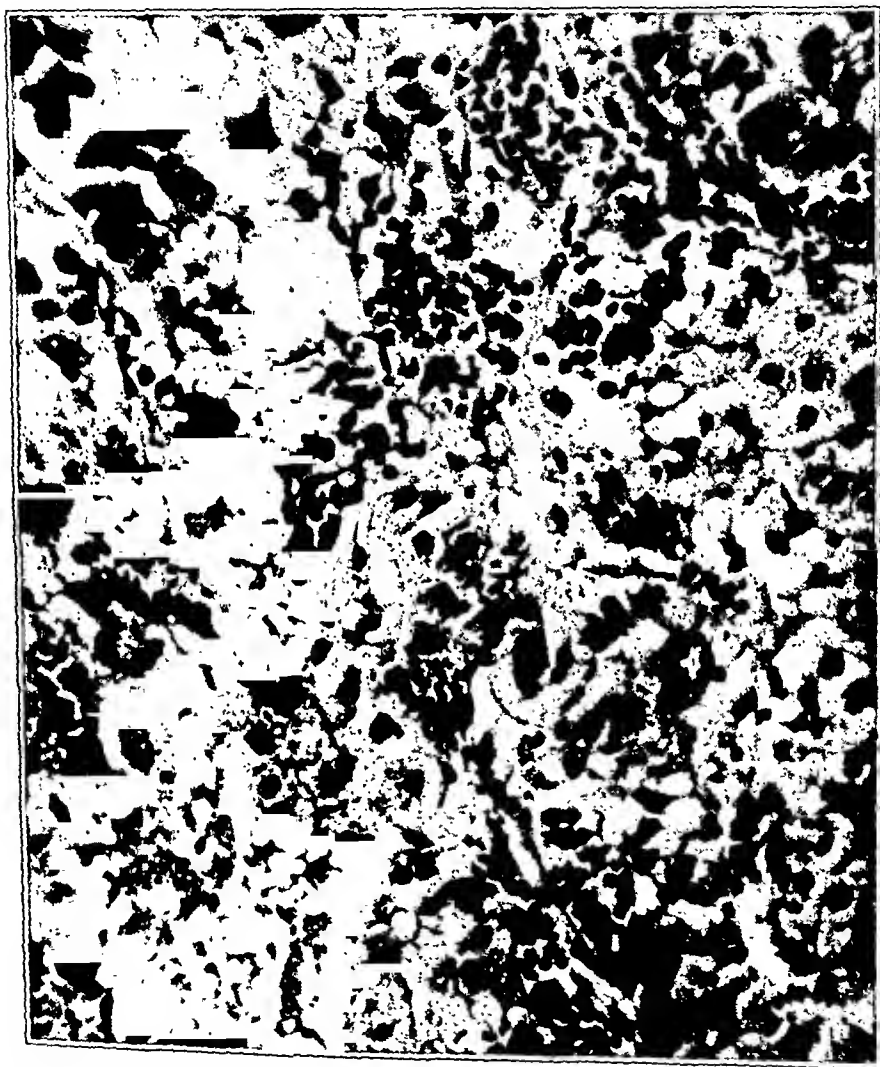


Fig. 7.—High power photomicrograph showing more detail of the individual cells in figure 6.

to lie near one end of the cell. The predominant cell then was a vacuolated oxyphil cell, or, as Castleman and Mallory designated it, a "transition *wasserhelle*." These cells were arranged in irregular tubules and in small alveoli in some places, and also, even in the most solid portions, there were small cysts. The central portions of the tumor were almost entirely cystic, with finger-like processes of the

cells extending throughout the cystic areas. There was little stroma throughout the tumor, and the most solid portions were quite vascular, large dilated blood spaces being seen between the tubules. It seems that this parathyroid adenoma should be designated as a transition *wasserhelle* cell type.<sup>5</sup>

A diagnosis was made of cystic degeneration and hemorrhagic adenoma in the lower pole of the right lobe of the thyroid gland. The thyroid gland was normal.

Immediately after operation, auricular fibrillation developed. Digitalis was given, and regular rhythm was restored within eight hours. The following morning the patient felt better than she had for a year. Pains previously complained of in the back and legs had entirely disappeared, and she could lift her feet from the bed without pain for the first time in months. Four days after operation, however, she complained of a peculiar sensation in her hands, but no definite carpopedal spasm was present. Chvostek's sign was positive, but Trousseau's sign was negative. Ten cubic centimeters of calcium gluconate was given intravenously. Carpopedal spasm developed the same night, and the patient complained of a "dead feeling" over the entire body. This again was relieved by 10 cc. of calcium gluconate. Mild attacks of tetany continued for the next three days, at which time treatment was started with calcium lactate, viosterol, calcium gluconate and parathyroid extract. She improved rapidly and was discharged on April 14, one month after operation.

At home she received 20 grains (1.3 Gm.) of calcium lactate three times a day, 10 drops of viosterol (containing 10,000 U. S. P. XI units of vitamin D per gram) three times a day and 1 cc. (20 units) of parathyroid extract each day. The serum calcium content showed a tendency to fall unless parathyroid extract was administered daily.

The results of determinations of calcium, phosphorus and phosphatase during observation are tabulated and graphically represented (fig. 2).

On April 27, seventeen days after discharge, the patient reentered the hospital for three days of observation and treatment. She complained of nausea and felt nervous and shaky. Chvostek's sign was positive. Calcium gluconate administered intravenously gave relief. Studies of the blood the day after admission showed 7.2 mg. of calcium, and 2.86 mg. of blood phosphorus per hundred cubic centimeters of blood and 4.18 units of phosphatase. The patient was discharged on April 30 feeling much improved. She was again placed on a regimen of viosterol, calcium lactate and parathyroid extract.

On June 24 she again reentered the hospital, with the history of having vomited for two weeks and of having paroxysms of choking and dyspnea. She had been

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5. Castleman and Mallory (The Pathology of the Parathyroid Gland in Hyperparathyroidism, *Am. J. Path.* 11:1-72, 1935) stated: "The neoplasias of the glands serve to reinforce the arguments against generically different cell types and favor the concept of a fundamental cell from which all others are derived. Pure tumors of either the oxyphil or wasserhelle type unaccompanied by any chief cell forms were not present in our series, and we find the occasional reports in the literature unconvincing. When cells of either of these specialized types are predominant numerous transition forms of the chief cell can always be demonstrated. The chief cell in other words is the only invariable component of a tumor, obviously the basic fundamental cell and possibly the only proliferative form. The other cell types derived from it are to be regarded as degrees of differentiation or as involution forms."

under the care of her family physician during the interval. Carpopedal spasm had repeatedly been present, and she was so weak that she was unable to leave her bed. She had kept nothing down that was taken by mouth for three days, and for the past thirty-six hours she had been having frequent paroxysms of dyspnea, during which time she could hardly get her breath. At these times she choked and had a feeling of the presence of phlegm in her throat that she was unable to raise.

On examination, she appeared drowsy and mentally sluggish, although she was conscious and perfectly rational. The pulse was weak but regular, and there was a slight tachycardia. There was evidence of moderate dehydration. Chvostek's sign was strongly positive; but Trousseau's was negative. She was able to retain little that was given by mouth.

During the first night of her admission she became very cold and clammy, and it was impossible to detect her pulse. No true tetany was observed; but 10 cc. of calcium gluconate was given intravenously. No appreciable effect was noted. The pulse remained of poor quality during the remainder of the night and the following day. On the second day of her admission the serum calcium content was 5 mg. and the phosphorus content 5.27 mg. per hundred cubic centimeters; there was 8.73 units of phosphatase. The patient was having repeated small emeses. Her body was cold and clammy, yet subjectively she felt warm. The pulse remained feeble, and the blood pressure was unobtainable most of the time in spite of the parenteral administration of fluids and calcium gluconate intravenously. The third day she was given 20 units of parathyroid extract, with some temporary improvement. Two parathyroid glands which had just been removed during the course of thyroidectomy on another patient were implanted in the rectus muscle, as first suggested by Halsted.<sup>6</sup>

As the patient was retaining nothing by mouth, the problem of vitamin D intake presented itself. This was attempted by administering it intramuscularly, by rectum and intranasally by means of a nasal spray. The amounts and frequency of the administration of parathyroid extract and calcium gluconate were increased, but apparently without effect, as she continued to have longer and more frequent periods of circulatory collapse. Generalized edema developed, which was felt to be on a nutritional and possibly thyroid deficiency basis. Four days before death therapy with thyroid extract and digalen was begun, which apparently had no effect, as the patient became rapidly worse, death occurring on the thirteenth day of admission, approximately four months after the original operation. The calcium content remained persistently low, while the phosphorus content rose to a high level of 7.2 mg., yet no tetany occurred.

The following conditions were discovered at autopsy: osteitis fibrosa cystica, hemorrhagic diathesis, bilateral hydrohemothorax, atelectasis of the lower lobe of the right lung, calcareous deposits in the renal tubules and total edentia.

In a careful search of the literature I was able to find over one hundred and twenty-five cases of proved hyperparathyroidism in which a parathyroid adenoma was found and removed in whole or in part. Eleven of the patients were dead at the time of the report (nine women

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6. Halsted, W. S.: Transplantation of the Parathyroid Glands, *Proc. Path. Soc. Philadelphia* 11:109-114, 1908.

and two men). Seven of these<sup>7</sup> exhibited signs of parathyroid tetany, and three eventually died, undoubtedly, from the effects of hypoparathyroidism. Renal complications, no doubt secondary to the effects of hyperparathyroidism, were responsible for four deaths.<sup>8</sup> Unexpected cardiac complications were the cause of two deaths.<sup>9</sup> One patient died a few years after operation from causes not stated,<sup>10</sup> and the remaining patient<sup>11</sup> died suddenly one night from suffocation, seven months after operation.

The case reported from the Henry Ford Hospital has been presented not only on account of the rarity of the condition but on account of the following interesting points:

1. The inclusion of a cystic parathyroid adenoma entirely within the lobe of the thyroid.

2. The demonstration of osteoporosis of the femur at the time of fracture, two and one-half years before the diagnosis of hyperparathyroidism was made. We were fortunate in being able to obtain this roentgenogram from another hospital. In contrast to this osteoporosis, our roentgenograms show a fully developed picture of osteitis fibrosa

7. (a) Beck, A.: Aussprache, Arch. f. klin. Chir. **152**:123-124, 1928. (b) Rosedale, R. S.: Fibrocystic Disease of the Bones Associated with Tumor of a Parathyroid Gland, Am. J. Path. **8**:745-751, 1932. (c) Albright, F.; Baird, P. C.; Cope, O., and Bloomberg, E.: Studies on the Physiology of the Parathyroid Glands: IV. Renal Complications of Hyperparathyroidism, Am. J. M. Sc. **187**:49-65, 1934. (d) Richardson, E. P.; Aub, J. C., and Bauer, W.: Parathyroidectomy in Osteomalacia, Ann. Surg. **90**:730-741, 1929. (e) Hannon, R. R.; Shorr, E.; McClellan, W. S., and DuBois, E. F.: A Case of Osteitis Fibrosa Cystica (Osteomalacia) with Evidence of Hyperactivity of the Parathyroid Bodies; Metabolic Study: I, J. Clin. Investigation **8**:215-227, 1930. (f) Bauer, W. K.; Albright, F., and Aub, J. C.: Metabolic Study: II, *ibid.* **8**:229-248, 1930. (g) McClellan, W. S., and Hannon, R. R.: Metabolic Study: III, *ibid.* **8**:249-258, 1930. (h) Albright, F.; Bauer, W.; Claffin, D., and Cockrill, J. R.: Studies in Parathyroid Physiology: Effect of Phosphate Ingestion in Clinical Hyperparathyroidism, *ibid.* **11**:411-435, 1932. (i) Wilder, Camp, Robertson and Adams.<sup>2</sup>

8. Churchill, E. D., and Cope, O.: The Surgical Treatment of Hyperparathyroidism Based on Thirty Cases Confirmed by Operation, Ann. Surg. **104**:9-35, 1936.

9. Babcock, W. W.: Multiple Giant-Celled Tumor of Bone, Osteitis Fibrosa Cystica, Paget's Type of Skull, and Renal Calculi, Apparently Due to Large Deeply Placed Parathyroid Tumor, S. Clin. North America **12**:1387-1392, 1932. Sorensen, Anshelm: Un cas de ostéite fibreuse généralisée traitée par l'enlèvement d'une tumeur parathyroïdienne, Acta chir. Scandinav. **74**:485-490, 1934.

10. Gutman, A. B.; Swenson, P. C., and Parsons, W. B.: The Differential Diagnosis of Hyperparathyroidism, J. A. M. A. **103**:87-94 (July 14) 1934.

11. Eggers, quoted by Mandl, F.: Therapeutischer Versuch bei einem Falle von Ostitis fibrosa generalisata mittels Exstirpation eines Epithelkoerperchentumors, Zentralbl. f. Chir. **53**:260-264, 1926; **56**:1739-1745, 1929.

-cystica. Lahey and Haggart<sup>12</sup> have pointed out that osteoporosis may exist as an early stage of the typical osteitis fibrosa cystica of Recklinghausen, as seen in hyperparathyroidism.

3. The development of tolerance or immunity by a patient to parathyroid extract.

4. A possible explanation of the cause of this tolerance to parathyroid extract.

There seems to be little doubt that in the three patients whose histories we have abstracted hypoparathyroidism resulted from the operation, and in two of the patients hyperparathyroidism was changed to hypoparathyroidism. The operation resulted in a disturbance of the calcium-phosphorus metabolism. Parathyroid extract was administered to each of these patients. Its physiologic effect, according to Aub,<sup>13</sup> is (1) to raise the blood calcium and lower the blood phosphorus, (2) possibly to increase the ionized calcium in the blood; (3) to increase the excretion of calcium and phosphorus in the urine, and (4) to obtain the calcium for this increased demand either from a large amount of ingested calcium or from the stores in the bone.

Each of these three patients received immediate benefit from the use of parathyroid extract. Wilder's<sup>2</sup> patient and our patient were given calcium salts and some preparation of vitamin D. After a time each of the patients again became worse and died, though theoretically their deficiency was being replaced. These deaths are apparently due to the gradual loss of the response to parathyroid extract. This failure did not become apparent for several months.

Collip<sup>14</sup> stated that "a state of lowered reactivity, of increased resistance or of actual non-responsiveness may gradually become manifested in those that have been treated for a long period with some glandular extract." He expressed the belief that the inhibitory substance which is found in the blood of animals after prolonged treatment with some hormone extract is a normal constituent of the blood. With prolonged injections of such an extract there would then be an increased production of the respective inhibitory principle. Therefore the danger is present in the use of parathyroid extract of actually adding to the gravity of the condition by causing "an over-production of the inhibitory principle as a result of too persistent treatment."

12. Lahey, F. H., and Haggart, G. E.: Hyperparathyroidism: Clinical Diagnosis and Operative Technique of Parathyroidectomy, *Surg., Gynec. & Obst.* **60**: 1033-1051, 1935.

13. Aub, J. S.: Glandular Physiology and Therapy: Parathyroid Hormone Therapy, *J. A. M. A.* **105**:197-199 (July 20) 1935.

14. Collip, J. B.: Inhibitory Hormones and Principle of Inverse Response, *Ann. Int. Med.* **8**:10-13, 1934.



Different groups of workers, Katzman, Wade and Doisy,<sup>15</sup> and Du Shane, Levine, Pfeiffer and Witschi,<sup>16</sup> have failed to find any anti-hormones. Twombly<sup>17</sup> expressed the belief that these substances are protein antibodies for precipitins to the hormone as an antigen can be demonstrated in the immune serums, and hormones inactivated partially by heat or completely by aging seem to be about as efficient in bringing about the formation of these protective substances as active preparations of the hormone. The fact, however, remains that gradually increasing doses of parathyroid extract had to be given in these cases we are reporting and yet with decreasing effect. Moehlig, Murphy and Reynolds<sup>18</sup> have found in their experimental work on dogs that immunity to large doses of parathyroid extract, as measured by the blood calcium, was soon established. Moehlig, in a personal communication, reported a case of hypoparathyroidism in which over \$1,200 was spent for parathyroid extract in a year and the patient still required increasing doses. According to Aub,<sup>13</sup> viosterol acts on the body much as parathyroid extract.

Dr. George R. Sharpless,<sup>19</sup> of the laboratory of the Henry Ford Hospital, in a study of the relation of vitamin D and parathyroid extract fed dogs carefully controlled synthetic diets. He has found that:

1. Normal dogs fed either a diet high in calcium and low in phosphorus or a diet with a normal calcium-phosphorus ratio have extensive deposits of calcium in the soft tissues when given viosterol and parathyroid extract but do not have deposits of calcium in the soft tissues when given parathyroid extract alone.

2. Normal dogs acquire a tolerance (immunity?) to parathyroid extract only when in a state of avitaminosis D and do not acquire a tolerance to parathyroid extract when vitamin D is supplied.

3. It is indicated that parathyroid extract may be impotent in the absence of vitamin D.

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15. Katzman, P. A.; Wade, N. J., and Doisy, E. A.: Concerning the Production of Anterior Pituitary Inhibitory Substances, *J. Biol. Chem.* **56**:lvi-lvii, 1936.

16. Du Shane, G. P.; Levine, W. T.; Pfeiffer, C. A., and Witschi, E.: Experimental "Constant Oestrus" and the Notion of Anti-Gonadotropic Hormones, *Proc. Soc. Exper. Biol. & Med.* **33**: 339-345, 1935.

17. Twombly, G. H.: Studies of the Nature of Antigonadotropic Substances, *Endocrinology* **20**:311-317, 1936.

18. Moehlig, R. C.; Murphy, J. M., and Reynolds, L.: Attempt to Produce Paget's Disease by Use of Anterior Pituitary Growth Extract and Parathyroid Extract Calcium Deposits in Kidney and Massive Calcium Deposits in Bone Marrow Produced by These Extracts, *Am. J. Roentgenol.* **34**:465-474, 1935.

19. Presented before the American Society of Experimental Pathologists, 1935.

## COMMENT

In our case, owing to vomiting toward the end of her life, the patient did not receive vitamin D. Just how far the use of ultraviolet rays may have replaced this deficiency we cannot say. In view of Dr. Sharpless' finding in our laboratory, we believe that every effort should be made to promote the use of vitamin D preparations in cases similar to those reported, as his finding is very clear in that a tolerance to parathyroid extract develops in the absence of vitamin D. While vitamin D should be used in the patients with hypoparathyroidism, it might by the same token be advisable to maintain the patient with hyperparathyroidism on a regimen high in calcium and low in vitamin D.

In a recent article, Bower and Mengle<sup>20</sup> reported two deaths from the additive effect of calcium and digitalis given simultaneously. Our patient received these two drugs simultaneously during the last five days of her illness, and it is possible that this may have been a factor in her death, although we are inclined to believe that it was not.

We criticize our operative treatment in that we tried to remove too much parathyroid tissue. Our error was made after examination of frozen sections of bits of tissue from the posterior capsule showed no parathyroid tissue and in our mistaken belief that the cystic nodule within the thyroid was a thyroid adenoma and not a parathyroid tumor.

Churchill<sup>21</sup> suggested an operation in stages, and we believe that this suggestion deserves careful consideration before any complete excision is done. Indications for such operations on the parathyroid glands may be as clearly worked out as they were for hyperthyroidism, though such operations for hyperthyroidism have become relatively less and less frequent as adequate preoperative preparation with iodine has been used.

It is not known whether the low serum calcium content or the high serum phosphorus content is responsible for the production of tetany, but the present tendency is to believe that the high serum phosphorus content is responsible, and so efforts to reduce this serum phosphorus would seem logical. This can be accomplished temporarily by the intravenous use of dextrose, as shown in the Henry Ford Hospital by Hartman and Foster.<sup>21</sup> Since it is almost impossible to reduce the amount of serum phosphorus by diet alone on account of the wide distribution of phosphorus in foods, recent efforts have been made to

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20. Bower, J. O., and Mengle, H. A. K.: The Additive Effect of Calcium and Digitalis: A Warning, with a Report of Two Deaths, *J. A. M. A.* **106**:1151-1153 (April 4) 1936.

21. Hartman, F. W., and Foster, D. P.: Clinical Evaluation of Blood Phosphate and Sugar Tolerance Curves: Analysis of Five Hundred Clinical Cases, *Am. J. Clin. Path.* **2**:289-297, 1932.

do this by mixing aluminum acetate with the foods of dogs and rats.<sup>22</sup> This precipitates the phosphorus as aluminum phosphate, which is not absorbed. Posterior pituitary probably should not be used in the treatment of meteorism in these patients, as it causes a rise in serum phosphorus.

#### CONCLUSIONS

Postoperative hypoparathyroidism should be a preventable condition.

Stage operations for hyperparathyroidism should be considered (Churchill).

Osteoporosis in hyperparathyroidism is an early stage of osteitis fibrosa cystica.

Parathyroid extract loses its influence when vitamin D is not present. A vitamin D preparation which could be administered either intravenously or subcutaneously would probably be of great value in cases of hypoparathyroidism complicated by extreme nausea and vomiting.

#### ABSTRACT OF DISCUSSION

DR. FRANK H. LAHEY, Boston: Thanks are due Dr. McClure for his frank discussion of this case, because every one here is going to have to face patients with parathyroid adenoma. There is not any question, if I consider my own experience, that a great many cases of hyperparathyroidism have probably been overlooked in the past years, as proved by the fact that within the last few years they are being found. I have no doubt that there were just as many cases in the past, but physicians did not know how to diagnose the condition. There are certain things about hyperparathyroidism that will accomplish definite results. There must be, I believe, some criteria as to the possible presence of the disease in order that the clinicians may suspect the possibility of this lesion and then turn the patient over to the laboratory workers to demonstrate whether or not it is present. In any patient who has unexplained pain referable to the nerve roots, hyperparathyroidism must be suspected; in any patient who has lost height owing to a round back, due in turn to the softening of the vertebral bodies and angulation at the weight-bearing point in the center of the back, possible hyperparathyroidism must be suspected. In any patient who has spontaneous fractures, demineralization of the bones, Recklinghausen's type of osteitis fibrosa cystica and kidney stones, one must investigate as to possible hyperparathyroidism. If a patient has a low phosphorus or a high calcium content of the blood and a high phosphatase content, it becomes the surgeon's problem. One of the first things a surgeon should have in mind regarding the removal of a parathyroid adenoma is that the adenoma is probably secreting most of the parathyroid extract and for some time after the removal of the adenoma there is likely to be a varying degree of tetany. In most cases in which my colleagues and I have removed a parathyroid adenoma, there has been tetany lasting up to a month; therefore, one must be prepared to handle these patients. If the tetany is too severe, it is difficult to treat. When the patient begins to complain of itching at the end of the nose and tingling in the fingers it is time to begin treatment instead of waiting until

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22. Jones, J. H.: The Relation of Serum Phosphate to Parathyroid Tetany, *J. Biol. Chem.* **114**:liv-lv, 1936.

the condition is too severe to manage. Knowing, then, that the patient with parathyroid adenoma probably will have tetany, the time to undertake the treatment is before it develops. Parathyroid adenomas do not occur in the typical places that used to be described in the textbooks. If they are not found in the usual places, they are in the thyroid or in the mediastinum. It is wise to have a pathologist make frozen sections at the time of exploration, and then good parathyroid glands will not be wasted, and parathyroid glands do not grow on every bush. When they are needed they are needed badly, and unfortunately it is not certain that transplantation is going to work. I think that the physician, particularly the urologist and the orthopedist, must be on the lookout for such tumors, and if this is done more will be discovered. If a parathyroid adenoma is removed, the bones of the patient will recalcify and he will be relieved of his symptoms.

DR. BRIEN T. KING, Seattle: I have enjoyed Dr. McClure's paper on this subject, having had a similar experience a number of years ago with a patient in whom chronic tetany developed after thyroidectomy for exophthalmic goiter. This patient was fairly satisfactorily relieved of symptoms of tetany during the early stage of the disease by the administration of parathyroid extract, but during the latter months of her illness it was quite ineffective in relieving the muscular spasms. In addition to the usual symptoms of tetany, angina pectoris developed. The attacks of pain always came on synchronously with attacks of tetany. Undoubtedly, the patient had tetany of the cardiac muscle and ultimately died during one of the spasms or cramps and anginal pain. As a result of this experience, I laid down the rule never to remove a parathyroid adenoma or other parathyroid tissue without first having searched for and identified normal parathyroid glands. With the following of this rule, in no case has hypoparathyroidism developed. The most common location for a parathyroid gland is at either superior pole, lying in close contact with the superior thyroid artery near its junction with the pole. If no normal parathyroid tissue is identified, I think that a portion of the adenomatous tissue sufficient to supply the needs of the body should be left in situ. While the subject of hyperparathyroidism is up for discussion, I want to issue a warning that indiscriminate removal of parathyroid tissue for rarefying bone disease will lead to disappointing results in those patients who do not have fairly typical clinical and laboratory findings.

DR. ROY D. McCLURE, Detroit: I did not have time to discuss as much as I should like the transplantation of parathyroid tissue which was done in this case. I was fortunate enough to be working in the Hunterian Laboratory when Dr. Halsted was doing his work on transplantation of parathyroid tissue. Halsted's law is that a gland will have a much better chance of "taking" as a transplant if there is a deficiency in that gland in the body. Ours was an ideal case for such a transplantation. Unfortunately, we waited until too late. The transplantation was done only five days before the patient died. The transplant was taken from a patient on whom I was performing a thyroidectomy that day, and we were able to transplant a parathyroid gland immediately. With regard to Dr. Lahey's discussion, I, too, feel that there must be many persons today who have parathyroid tumors that have not been diagnosed. I, personally, have had in the last two years two patients with parathyroid tumors that I operated on. The result in the last patient was simply a miracle, and the rheumatism for which this patient had been treated for a long time was cured. Dr. King is right in opposing operations in all groups of cases in which parathyroidectomy was advocated a few years ago. Not so long ago in Detroit a patient of ours put it up to the judge in the Compensation Court

to decide whether his condition, an ankylosing spondylitis (spondylose rhizomélisque or Marie-Strümpell's disease), was due to hyperthyroidism. Following the teaching of Oppel, Ballin and others, we had, in spite of the presence of fairly normal values for serum calcium, phosphorus and phosphatase, performed a subtotal parathyroidectomy on him. After operation the patient was subjectively better; objectively, he was not. In the Compensation Court he claimed compensation from one of the big companies in Detroit. He had been partially strangled by a fellow employee who fought with him while he was detaining this employe for the arrival of the police. From the evidence presented by more or less expert doctors on both sides, the judge in this court decided that the ankylosing spondylitis was due to hyperparathyroidism which had been caused by an injury to the man's neck while he was performing his work.

# SPINAL ANESTHESIA

## THE EXPERIMENTAL BASIS OF SOME PREVAILING CLINICAL PRACTICES

CoTUI, M.D.

NEW YORK

The purpose of this report is to examine various clinical practices in the use of spinal anesthesia and the assumption concerning them in the light of facts accumulated in a four year study on experimental spinal anesthesia in the dog. The following topics will be discussed: (1) the effect of the narcotic agent on the respiratory center; (2) the use of narcotics as premedication, (3) the effect of a stimulating drug (a 25 per cent solution of pyridine betacarboxic acid di-ethylamide) on paralysis of the respiratory center, produced by procaine hydrochloride, (4) the fall in blood pressure and its cause, effects and treatment, and (5) the use of carbon dioxide as a stimulant.

### EFFECT OF THE NARCOTIC AGENT ON THE RESPIRATORY CENTER

In a previous communication,<sup>1</sup> it was shown that if procaine hydrochloride is made to reach the medulla in sufficient strength, either by injection into the cisterna magna or by irrigation of the fourth ventricle, it causes paralysis of the respiratory center. This paralysis was found to be reversible, i. e., with the institution of adequate artificial respiration, spontaneous respiration reestablishes itself in little over an hour. It was further demonstrated that the conclusion of Koster and Kasman,<sup>2</sup> that procaine hydrochloride in a solution of 2.5 per cent applied to the medulla does not cause respiratory paralysis, was based on an error of experimental technic.

Velrs<sup>3</sup> and recently Thompson,<sup>4</sup> on the ground that large doses of procaine hydrochloride are required to paralyze the respiratory center

From the Laboratory of Experimental Surgery, Department of Surgery, New York University College of Medicine.

The Ciba Company supplied the pyridine betacarboxic acid di-ethylamide used for this study.

1. CoTui, F. W.: Experimental Studies on Subarachnoid Anesthesia, *Surg., Gynec. & Obst.* **55**:290-297 (Sept.) 1932.

2. Koster, H., and Kasman, L. P.: Spinal Anesthesia for the Head, Neck and Thorax, *Surg., Gynec. & Obst.* **49**:617-629 (Nov.) 1929.

3. Velrs, G.: Heart Beat and Respiration in Total Novocaine Analgesia, *Northwest Med.* **30**:256 (June): 322 (July) 1931.

4. Thompson, K. W.: Spinal Anesthesia: An Experimental Study, *Surg., Gynec. & Obst.* **58**:852-866 (May) 1934.

of normal animals, expressed doubt whether this complication occurs in clinical spinal anesthesia. This reasoning is unsound, as is shown by the fact that I found that the minimum lethal dose of procaine hydrochloride cisternally, i. e., for the respiratory center, while relatively constant for the unanesthetized normal animal,<sup>5</sup> is markedly reduced by narcosis produced by large doses of morphine, moderate doses of sodium amytal,<sup>6</sup> dial, pentobarbital sodium and morphine and chloralose.<sup>7</sup> It is likewise reduced by such factors as old age, dehydration,<sup>7</sup> infections and low blood pressure states induced by various means.<sup>8</sup> This last finding is significant in view of the possibility of the spinally injected drug reaching the center after it has caused a fall in blood pressure. Of interest, too, is the work of Richet<sup>9</sup> on the comparative pharmacology of cocaine. He found that the sensitivity of different species of animals to cocaine increases in proportion to the increasing development of the brain.

The finding that derivatives of barbituric acid reduce the lethal dose of procaine hydrochloride is at apparent variance with the work of Hofvendahl,<sup>10</sup> Tatum and his co-workers,<sup>11</sup> LaMendola<sup>12</sup> and Martin.<sup>13</sup> These authors showed that members of the barbituric acid series are antidotes for cocaine poisoning. The discrepancy, however, is more apparent than real. In cocaine poisoning caused by systemic administration the convulsive phase is the striking feature, whereas in that caused by direct application of the drug to the nervous tissue the paralytic phase is predominant. In the former case a depressant would be indicated, and in the latter, contraindicated.

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5. CoTui, F. W.: The Intracisternal Minimum Lethal Dose of Procaine-Hydrochloride (Novocaine) in Dogs, *J. Pharmacol. & Exper. Therap.* **48**:223-228 (June) 1933.

6. CoTui, F. W.: The Effect of Different Narcotics and Narcotic Combinations on the Minimum Lethal Dose of Procaine Hydrochloride Intracisternally, *J. Pharmacol. & Exper. Therap.* **48**:229-233 (June) 1933.

7. CoTui, F. W.: Unpublished results.

8. CoTui, F. W.: The Effect of Pathologic States on the Minimum Lethal Dose of Procaine Intracisternally, *J. Pharmacol. & Exper. Therap.* **50**:51-60 (Jan.) 1934.

9. Richet, C.: Les poisons convulsivants, *Arch. internat. de pharmacod.* **4**:293-309, 1898.

10. Hofvendahl, A.: Die Bekämpfung der Cocainvergiftung, *Ztschr. f. Hals-, Nasen- u. Ohrenh.* **1**:233-235, 1922.

11. Tatum, A. L.; Atkinson, A. J., and Collins, K. H.: Acute Cocaine Poisoning: Its Prophylaxis and Treatment in Laboratory Animals, *J. Pharmacol. & Exper. Therap.* **26**:325-335 (Dec.) 1925.

12. LaMendola, S.: Antagonismo tra sulfonale, trionale, veronale, veronale sodico, luminale sodico e cocaina, *Arch. di farmacol. sper.* **37**:256-268, 1924.

13. Martin, E. G.: Local Anesthetic Agents: Preventive and Emergency Treatment of Toxicity with Special Reference to Barbituric Acid Derivatives, *J. A. M. A.* **91**:555-557 (Aug. 25) 1928.

EFFECT OF STIMULANT ON PARALYSIS OF THE RESPIRATORY  
CENTER PRODUCED BY PROCAINE HYDROCHLORIDE

In view of the analeptic property of 25 per cent solution of pyridine betacarbonic acid di-ethylamide,<sup>14</sup> it was deemed desirable to determine its therapeutic value in animals in which the respiratory center had been paralyzed by a minimum lethal dose of procaine hydrochloride. Fifteen unanesthetized dogs were each given cisternally 1.5 mg. of procaine hydrochloride per centimeter of spinal length. This dose is a sure lethal dose.<sup>5</sup> It will be seen from table 1 that all the five dogs in the control group died, that two of the five in the group which were each

TABLE 1.—*Effect of a Stimulant on Unanesthetized Dogs with Paralysis of the Respiratory Center \**

Experiment No.	Weight, Kg.	Spinal Length, Cm.	Total Dose of Procaine Hydrochloride, Mg.	Dose of Stimulant Intravenously, Cc.	Result
1	14.25	74.0	111.0	0	Died
2	15.0	80.0	120.0	0	Died
3	14.5	76.0	114.0	0	Died
4	14.0	74.5	112.0	0	Died
5	18.0	81.0	121.5	0	Died
6	14.0	73.0	109.5	2	Died
7	14.0	79.0	118.5	2	Survived
8	14.5	76.0	114.0	2	Died
9	15.5	82.0	123.0	2	Died
10	16.0	76.0	114.0	2	Survived
11	15.5	82.0	123.0	5	Survived
12	16.0	86.0	129.0	5	Died
13	14.5	73.0	109.5	5	Survived
14	15.0	81.0	121.5	5	Survived
15	15.0	76.0	114.0	5	Died

\* Unanesthetized dogs were given 1.5 mg. of procaine hydrochloride per centimeter of spinal length intracisternally and then a 25 per cent solution of pyridine betacarbonic acid di-ethylamide intravenously.

given 2 cc. of the pyridine betacarbonic acid de-ethylamide lived and that three of the five in the group given 5 cc. lived. Figure 1 shows the kymogram of the sixteenth animal. In this experiment the fourth ventricle was irrigated with a solution of procaine hydrochloride (1 cc. of solution to 0.8 mg. of procaine hydrochloride) until the respiration ceased. The intravenous injection of 10 cc. of the stimulant in two doses of 5 cc. each restored the respiration.

14. Faust, E. S.: On Pyridine- $\beta$ -Carbonic Acid Diethylamide and Its Use as an Analeptic, *Lancet* 1:1336-1339 (June 27) 1925; Ueber Pyridin-Beta-Carbonsäure-Diäthylamid (Coramin) und dessen Verwendung als Analepticum, *Schweiz. med. Wchnschr.* 10:229-232 (March 6) 1924.



## CHANGES IN BLOOD PRESSURE

The hypotension which accompanies spinal anesthesia has been explained in several ways. Gray and Parsons<sup>15</sup> attributed it to relaxation of the muscles of the abdomen and the lower limbs and to paralysis of the intercostal muscles and the consequent diminution in the pumping power of the chest. Smith and Porter<sup>16</sup> considered splanchnic paralysis to be the cause, as did Schilf and Ziegner.<sup>17</sup> Bower and his co-workers<sup>18</sup>

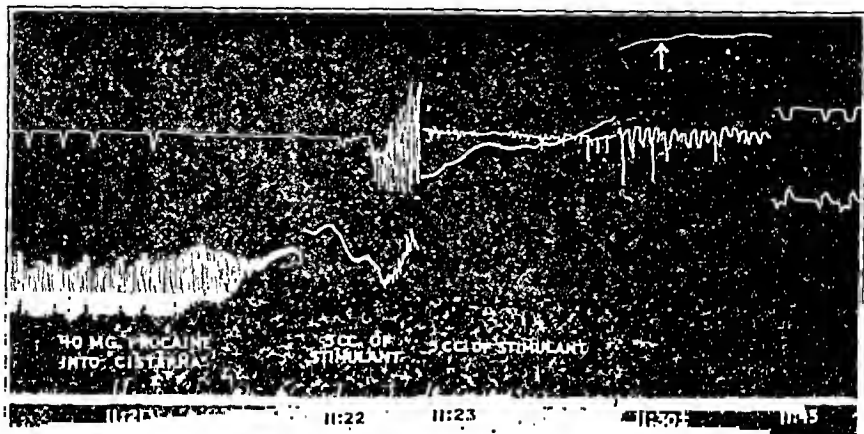


Fig. 1.—Kymogram of a dog weighing 18 Kg. and measuring 81 cm. in spinal length that was given subcutaneously 5 mg. of morphine hydrochloride per kilogram of body weight and intravenously 70 mg. of chloralose per kilogram of body weight. The upper tracing is a record of the respirations (pneumograph); the middle tracing of the blood pressure (cannula in the left femoral artery), and the lower tracing, the time in seconds. At 11:21 40 mg. of procaine hydrochloride was administered cisternally. Note the almost immediate respiratory paralysis. At 11:22 5 cc. of a 25 per cent solution of pyridine betacarboxylic acid di-ethylamide in water was given intravenously. Note the respiratory movements. These are exaggerated by convulsive movements. At 11:23 a second dose of the stimulant was given. Note the rise in blood pressure and the respiratory movements at the end of the strip. In the strip made at 11:30 the arrow indicates the blood pressure (a clot formed in the cannula). Note the spontaneous respiration. At 11:45 the respirations and the blood pressure were normal.

15. Gray, H. T., and Parsons, L. P.: Blood Pressure Variations Associated with Lumbar Puncture and the Induction of Spinal Anesthesia, *Quart. J. Med.* **5**:339-367 (April) 1912.

16. Smith, G. G., and Porter, W. T.: Spinal Anesthesia in the Cat, *Am. J. Physiol.* **38**:108-127 (July) 1915.

17. Schilf, E., and Ziegner, H.: Das Wesen der Blutdrucksenkung bei der Lumbalanesthetie, *Arch. f. klin. Chir.* **130**:352, 359, 1924.

18. Bower, J. O.; Clark, J. H.; Wagoner, G., and Burns, J. S.: Spinal Anesthesia, *Surg., Gynec. & Obst.* **54**:882-897 (June) 1932.

ascribed the fall partly to respiratory depression and partly to paralysis of the cardiac nerves. Ferguson and North<sup>19</sup> stated that the entire vasomotor system participates in vasodilatation and that the degree of depression of the blood pressure is in direct ratio to the number of white rami anesthetized.

My own circulatory studies are described here. Only police dogs of from 20 to 21 Kg. of body weight and of from 87 to 88 cm. in spinal length were used. These will be referred to as standard dogs. The drug was always injected into the first lumbar space in a volume of 2 cc., unless otherwise specified.

The typical blood pressure curve consists of: (1) a primary fall, (2) an intermediate rise and (3) usually a secondary fall.

These phases are shown in figure 2.

*The Primary Fall.*—The primary fall occurs before the injection is complete. It is accompanied by an increase in the volume of the hindleg (fig. 3) and a rise of its surface temperature, averaging 2 C. in the footpads. These changes indicate vasodilatation of the limb. This change in temperature has been shown by Morton and Scott<sup>20</sup> and by Gask and Ross,<sup>21</sup> who employed spinal anesthesia as a test of the vasomotor index of extremities with vascular disease. That the rise in surface temperature and therefore inferentially an increase in the volume of blood in the posterior extremities is effected mainly through the sympathetic nerves is evidenced by the following fact. In animals in which complete sympathectomy of one of the lower extremities has been performed, the surface temperature of that extremity is maximal after sympathectomy and does not rise further with spinal anesthesia. In the sound leg, however, the injection of the spinal anesthetic causes a prompt rise of surface temperature which soon reaches the level of that of the sympathectomized leg, as shown by figure 4.

The primary fall, then, is due to paralysis of vasomotor nerves which were reached by the original bulk of the injected fluid.

The extent of the primary fall as well as the duration is dependent more on the volume injected than on the dose of the drug. Thus, in table 2 it may be seen that 250 mg. of the drug in 2 cc. of solution produces a fall of almost the same depth and duration as 800 mg. in 2 cc.; that 250 mg. in 5 cc. produces a fall similar to 800 mg. in 5 cc.,

19. Ferguson, L. K., and North, J. P.: Observations on Experimental Spinal Anesthesia, *Surg., Gynec. & Obst.* 54:621-634 (April) 1932.

20. Morton, J. J., and Scott, W. J. M.: Studies on Activity of Lumbar Sympathetic Nervous System, *Ann. Surg.* 92:919-930 (Nov.) 1930.

21. Gask, G. E., and Ross, J. P.: The Surgery of the Sympathetic Nervous System, New York, William Wood & Company, 1934, p. 31.

but that the fall caused by 5 cc. of solution containing either dose is almost twice the depth and duration as with 2 cc. containing either dose. This is but to be expected since the larger the original bulk injected, the greater the number of spinal nerves paralyzed, and supra-effective concentrations cannot be more potent than already effective ones.

*The Intermediate Rise.*—The intermediate rise is due to vasoconstriction of the as yet unaffected part of the body in an effort to overcome the fall in blood pressure. Figure 3 shows that concomitant with the fall in blood pressure and the dilatation of the posterior extremity, there is a gradual decrease in the volume in the anterior extremity,

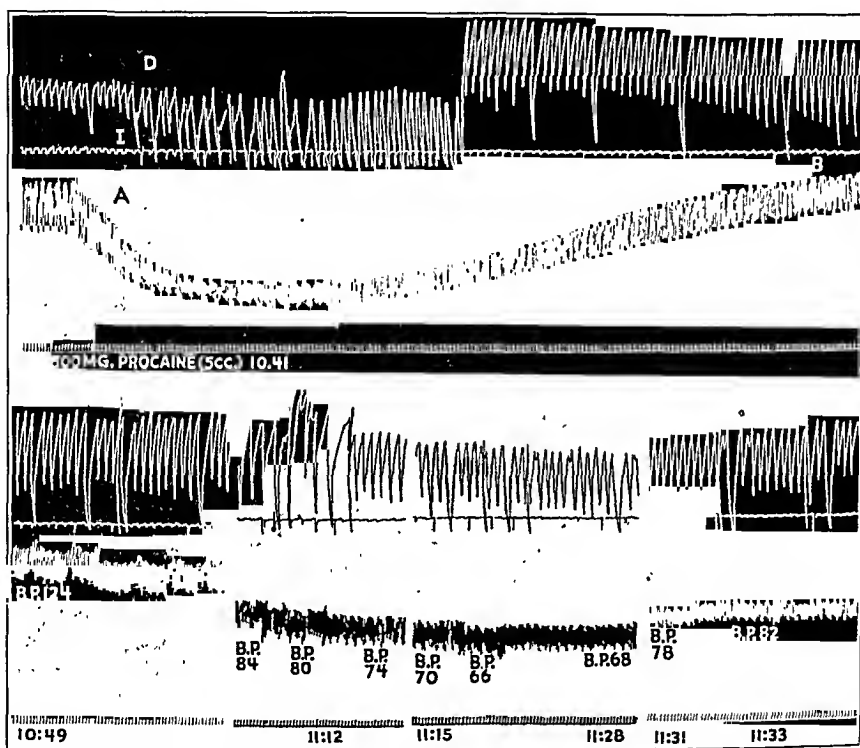


Fig. 2.—Tracing showing a typical blood pressure curve after spinal anesthesia produced by the injection of 300 mg. of procaine hydrochloride. The dog used weighed 19 Kg. and measured 87 cm. in spinal length. At 9:45 5 mg. of morphine hydrochloride per kilogram of body weight was given subcutaneously. Diaphragmatic breathing was recorded by a lever attached to the abdominal wall and is shown in tracing *D*. *I* is the intercostal tracing made with a thoracic pneumograph. The blood pressure was registered from the left femoral artery. In the strip made at 10:41 note the primary fall at *A* and the intermediate rise at *B*. At 10:49 the secondary fall is beginning. At 10:49, 11:12 and 11:15 the secondary fall is recorded. Note the trough of the fall to blood pressure. The strip made at 11:31 and 11:33 shows recovery of the blood pressure.

which reaches its maximum with the peak of the intermediate rise. The injection of a larger volume of the drug apparently reached a sufficiently high level to paralyze the vasoconstrictors of the anterior extremity, shown in figure 3, made at 3:50 and later. No compensatory rise was evident. Also, flooding the nerves along the entire length of the spinal canal with the anesthetic solution abolishes the compensatory rise, as is shown in figure 5. This compensatory effort is probably brought about by the carotid sinus and aortic nerve mechanism. The completeness of the compensation depends on the extent and the efficiency of the as yet unaffected vasomotor nerves, since the peak of the intermediate rise is lower with larger than with smaller injected volumes.

The injected volume remaining equal, the kind of premedication determines the rapidity of the intermediate rise. Thus, it is slowest with morphine and ether, next with sodium amytal, pentobarbital sodium

TABLE 2.—*Comparative Effect of Dose and Volume of Drug Injected on the Blood Pressure*

Experiment No.	Dose of Procaine Hydrochloride, Mg.	Volume Injected, Cc.	Initial Blood Pressure Mm. of Hg	Lowest Blood Pressure (Primary Fall), Mm. of Hg	Time from Injection to Crest of Intermediate Rise, Sec.
1	800	2	125	90	100
2	250	2	115	86	80
3	800	5	120	50	210
4	250	5	110	51	180

and morphine and chloralose and most rapid with dial and ethyl carbamate. This probably means that the reactivity of the sympathetic system to a fall in blood pressure is modified by the preliminary administration of the narcotic. Stated in other words, the efficiency of the compensatory mechanism is impaired in different degrees by different narcotics.

*The Secondary Fall.*—With smaller doses of the drug the secondary fall may be absent. It begins from five to twenty-five minutes after the injection and lasts for a more prolonged period than the two previous phases. It is ascribed to the gradual spread of the drug upward, paralyzing the vasomotor nerves one by one so that not enough of the body is left unparalyzed to maintain a normal blood pressure. The relation of the dose to the extent of the fall and the duration of the period before the blood pressure is restored to the 100 mm. level is shown by table 3. The extent of the secondary fall is also related to the position of the animal. The dose and volume remaining the same, the secondary fall is deepened and prolonged by the Trendelenburg position, as may be

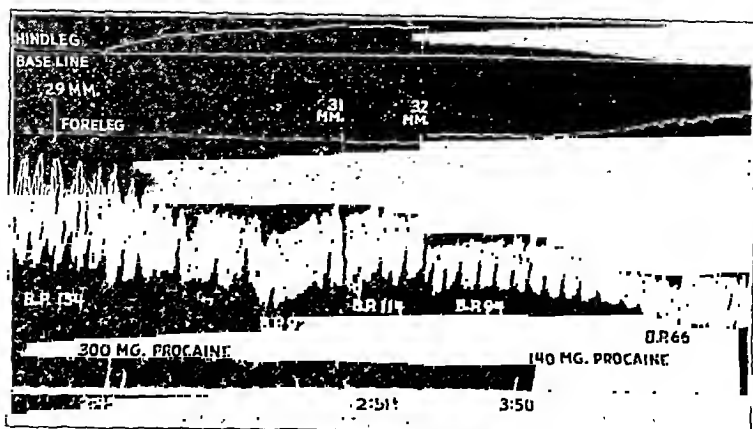


Fig. 3.—Kymogram of a dog weighing 21 Kg. and measuring 89 cm. in spinal length. At 2:45 when the initial blood pressure was 134, 300 mg. of procaine hydrochloride in 2 cc. of water was injected into the spinal canal at the twelfth thoracic space. Note that concomitant with the primary fall there is an increase in the volume of blood in the hindleg and a decrease in that of the foreleg. The decrease in the volume of blood of the foreleg is maximal at 2:51, the peak of the intermediate rise. At 3:50 140 mg. of procaine hydrochloride in 5 cc. of water was injected into the same space. Note the further fall in the blood pressure, an increase in the volume of blood in the foreleg and a decrease of that in the hindleg parallel with the blood pressure.

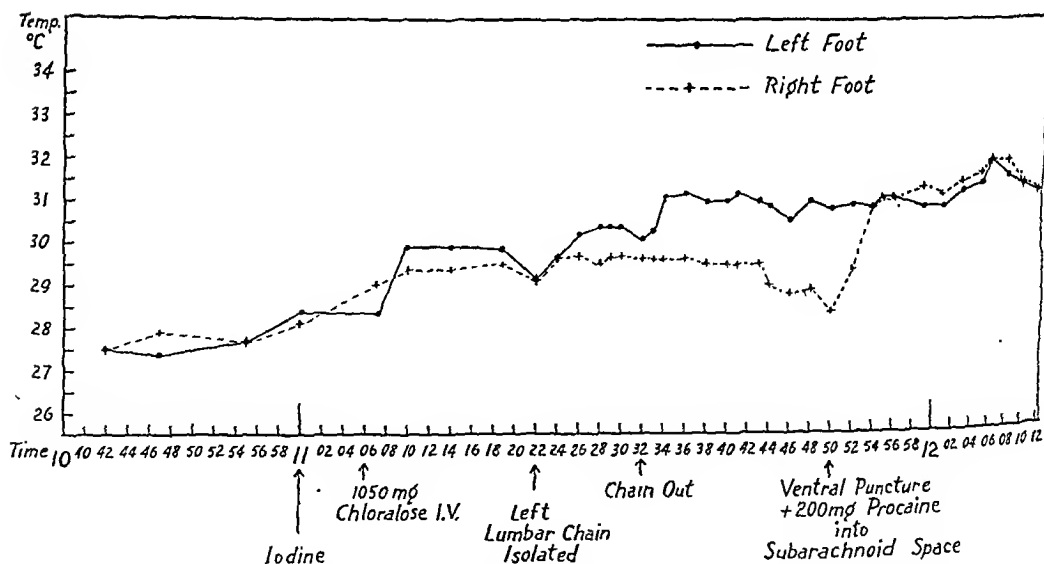


Fig. 4.—Curves showing temperature response caused by sympathectomy in dog 22, a female, weighing 15 Kg. Morphine hydrochloride, 5 mg. per kilogram of body weight, was administered subcutaneously and chloralose, 70 mg. per kilogram of body weight, intravenously. Note (1) the rise in surface temperature of both extremities after the administration of chloralose intravenously, (2) the rise in the surface temperature of the left footpad on isolation of the left lumbar chain and the further rise when the chain was removed, (3) and the rise in surface temperature of the right footpad after spinal anesthesia.

seen in table 4. This result is to be expected, since the Trendelenburg position allows a more cephalad spread of a hyperbaric solution.

*Comment.*—This typical curve is modified by the occurrence of respiratory paralysis. The blood pressure in this case describes a fairly swift arc to zero (fig. 6). This paralysis may occur in any of the three phases. Artificial respiration restores it to its level previous to the occurrence of this complication (fig. 6). This swift fall of blood

TABLE 3.—*Relation of the Dose of the Drug to the Fall in Blood Pressure and Length of Period Before Recovery*

Experiment No.	Total Dose of Procaine Hydrochloride, Mg.	Lowest Blood Pressure, Mm. Hg	Time of Recovery to 100 Mm. Hg, Min.
1.....	250	96	52
2.....	300	65	74
3.....	600	52	106
4.....	760	36	134
5.....	800	22	192

\* Morphine sulfate (2 mg. per kilogram of body weight subcutaneously) and ether were given preliminary to the administration of the spinal anesthetic.

TABLE 4.—*Relation of Position to Secondary Fall in Blood Pressure*

Head Down		Horizontal	
Initial Blood Pressure, Mm. of Hg	Minimum Blood Pressure, Mm. of Hg	Initial Blood Pressure, Mm. of Hg	Minimum Blood Pressure, Mm. of Hg
120	80	118	96
100	76	102	86
116	72	114	78
125	86	125	92
102	72	102	82
108	76	108	84
112	78	110	78
112	76	112	84

\* Dogs weighing 20 Kg. and measuring 65 cm. in spinal length were each given 400 mg. of procaine hydrochloride in 3 cc. of water intraspinally.

pressure will be explained in the section on the administration of carbon dioxide.

That this pattern of blood pressure curve is not identical with that obtained on human beings during spinal anesthesia may be seen by comparing it with figure 7. Whether the transience of the primary fall is missed in the intermittent method of sphygmomanometry or whether the difference in the curvatures of the human and canine spines accounts for the divergence has not as yet been ascertained but is being investigated.

As evidence of splanchnic dilatation, changes in intestinal volume are not reliable. For while the vessels themselves may undergo dilatation, the intestinal muscle undergoes contraction in response to the release of sympathetic inhibition, thus bringing two opposing factors into play. A better index of splanchnic dilatation is given by changes in the size of the spleen. This organ was shown by Barcroft<sup>22</sup> to be one of the principal visceral organs for circulatory homeostasis. It dilates in time of rest to accommodate excess blood and contracts in time of emergency to expel blood into the circulation. According to Buljak<sup>23</sup> and Schafer

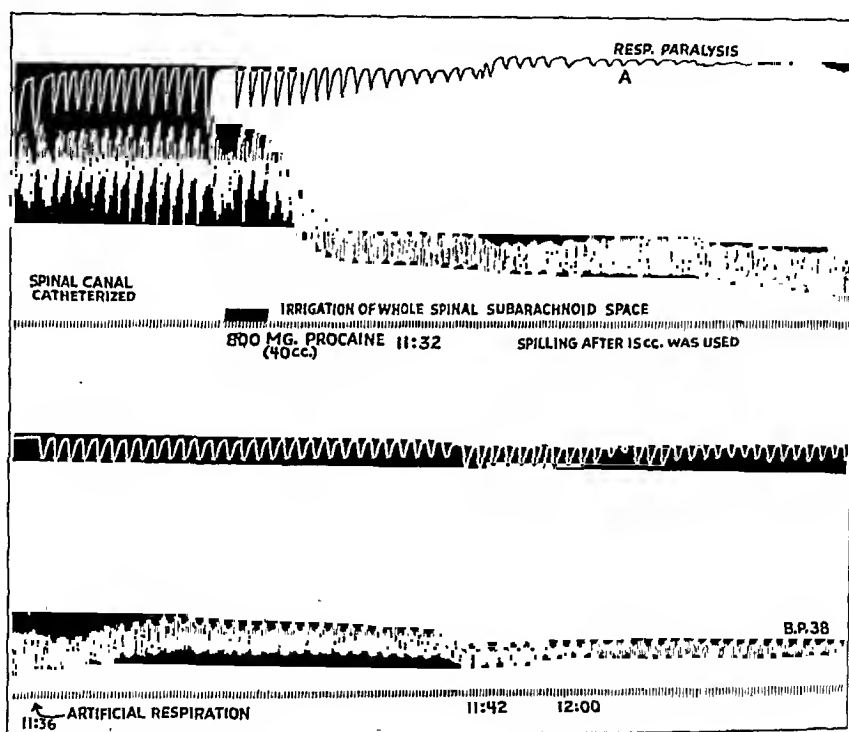


Fig. 5.—Tracing showing the absence of an intermediate rise by irrigation of the entire spinal subarachnoid space with procaine hydrochloride. The dog used weighed 18 Kg. and measured 86 cm. in spinal length. At 10:45 5 mg of morphine sulfate per kilogram of body weight was administered subcutaneously. At 11:00 ether was started. At from 11:08 to 11:28 the cisterna magna was opened and the spinal subarachnoid space was catheterized with a ureteral catheter. Respiratory paralysis supervened at *A* and modified the curve somewhat. At 11:36 there was a slight rise after artificial respiration and at 11:42, the usual secondary fall.

22. Barcroft, J.: Recent Knowledge of the Spleen, *Lancet* 1:319-322 (Feb. 11) 1925.

23. Buljak, J.: Ueber die Contractionen und die Innervation der Milz. *Virchows Arch. f. path. Anat.* 69:181-213, 1877.

and Moore<sup>24</sup> it is supplied by vasoconstrictors from the third thoracic to the first lumbar segment, chiefly from the fifth to the tenth thoracic segment.

Normally, as may be seen from table 5, the mean ratio of splenic weight to body weight is  $1.3 \text{ to } 2.7 \times 10^{-3}$ . In spinal anesthesia, the spleen becomes from four to five times its normal size. Figure 8 shows a section of the spleen before spinal anesthesia, and figure 9, one after spinal anesthesia. Note that the latter is packed with red blood cells. Figure 10 shows three views of the same spleen under the following

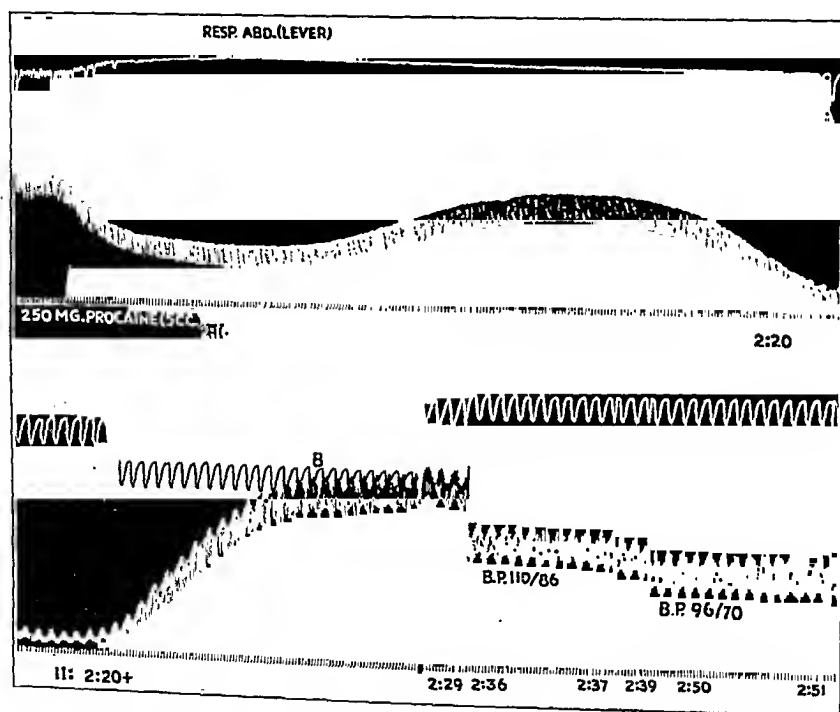


Fig. 6.—Tracing showing the modification of the typical blood pressure curve by respiratory paralysis. The dog used weighed 16 Kg. and measured 84 cm. in spinal length. At 1:50 5 mg. of morphine per kilogram of body weight was administered subcutaneously. At 2:08 ether was started. In the strip made at 2:16 note the primary fall and intermediate rise. Note the gradual fall after complete respiratory paralysis. Artificial respiration was started at A. In the strip made at 2:20 note the rise in blood pressure at B to above normal. The abdominal lever was readjusted here and in the next tracing. At 2:29 there was a secondary fall.

conditions: (a) after medication with morphine and chloralose, (b) after spinal anesthesia and (c) after the intravenous injection of 1 mg.

24. Schafer, E. S., and Moore, B.: On the Contractivity and Innervation of the Spleen, *J. Physiol.* 20:1-50 (June) 1896.



of ephedrine hydrochloride per kilogram of body weight. It is thus shown that the splanchnic vessels also undergo vasodilatation.

As to whether the abolition of the respiratory excursions of the thorax as a result of intercostal paralysis is responsible for the fall in blood pressure, the following experiment devised for another purpose by Dr. E. A. Rovenstine is interesting. The lungs of a dog under morphine and chloralose anesthesia were irrigated through a tracheal tube with pure oxygen until complete apnea was produced. It is seen (fig. 11) that there is no fall in blood pressure with the cessation of respiratory movements. The component which the thoracic excursions contribute to the homeostasis of blood pressure is at best a minor one, and with a normally functioning vasomotor mechanism the effect of its absence is negligible.

The question of the cause of the fall in blood pressure may now be answered. It is due to the paralysis of the vasomotor nerves of

TABLE 5.—*Effect of Spinal Anesthesia on the Spleen*

Weight of Spleen*	
Normal	Under Spinal Anesthesia
2.69	10.67
2.36	7.3
2.2	14.6
2.8	8.5
1.3	14.8
2.8	
1.8	Average 11.17
2.2	
Average 2.27	

\* To obtain body weight ratio multiply the ratio by  $10^{-3}$ .

the segments anesthetized, with the consequent dilatation of the vessels, somatic as well as visceral. The resulting increase of the vascular tree makes the existing blood volume inadequate. Thoracic paralysis may contribute its share in the latter part of the anesthesia, either through abolition of the suction effect of the chest or through an accumulation of carbon dioxide. But this is not primary and may at best be only a contributory factor. Neither can the paralysis of the cardiac nerves be considered primary or immediate, as hypothecated by Bower and his co-workers.<sup>18</sup> The fact that only in those of their cases in which the level of anesthesia has reached the level of the cardiac nerves is there a marked fall in pressure is inconclusive evidence that it is primarily the paralysis of the cardiac nerves which causes the low blood pressure. It only means that more vasomotor nerves are paralyzed and the less unaffected nerves are left to compensate for the fall.

## EFFECTS OF THE LOW BLOOD PRESSURE

In this set of experiments, standard animals were given 5 mg. of morphine hydrochloride per kilogram of body weight subcutaneously fifteen minutes before they were put on the experimental table. There they were anesthetized lightly with ether while the femoral artery was being cannulated for measurement of the blood pressure and lumbar puncture performed, both procedures together taking less than fifteen minutes. The administration of ether was discontinued, and the animal was allowed to lie quietly for ten minutes. A control set of blood samples was then taken. The spinal anesthetic was injected, and the blood pressure was allowed to fall gradually to below 80 mm. Artificial respiration was started so as to avoid any asphyxia. After the blood pressure had been under 80 mm. for an hour, the second set of blood samples was taken. Arterial oxygen and venous oxygen and lactic acid were determined from the blood samples.

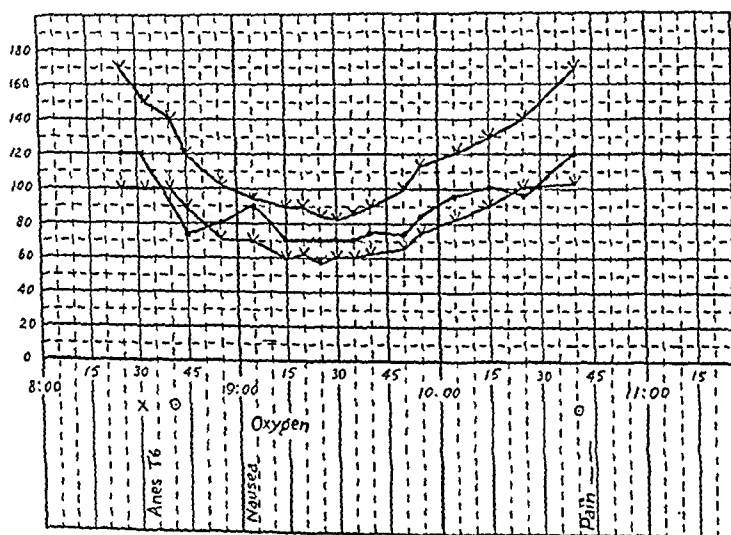


Fig. 7.—The blood pressure curve during spinal anesthesia in a clinical case, in which amputation of the cervix, repair of a cystocele and perineorrhaphy were performed (adapted from Waters and Rovenstine). The following code is used: the solid dot, the pulse rate; the circle, the respiratory rate;  $\nabla$ , the blood pressure; the circle and dot, operation; and X, anesthesia.

Table 6 shows that in the hypotension of spinal anesthesia, even though the oxygen content of the arterial blood may be slightly raised by artificial respiration, there is a lowered oxygen content of the venous blood. This finding corresponds with that of Aub and Cunningham<sup>25</sup> in experimental traumatic shock. On account of the sluggish circulation due to the low blood pressure, oxygen is not delivered in sufficient

25. Aub, J. C., and Cunningham, T. D.: Studies in Experimental Traumatic Shock: II. The Oxygen Content of the Blood, *Am. J. Physiol.* **54**:408-415 (Dec.) 1920.

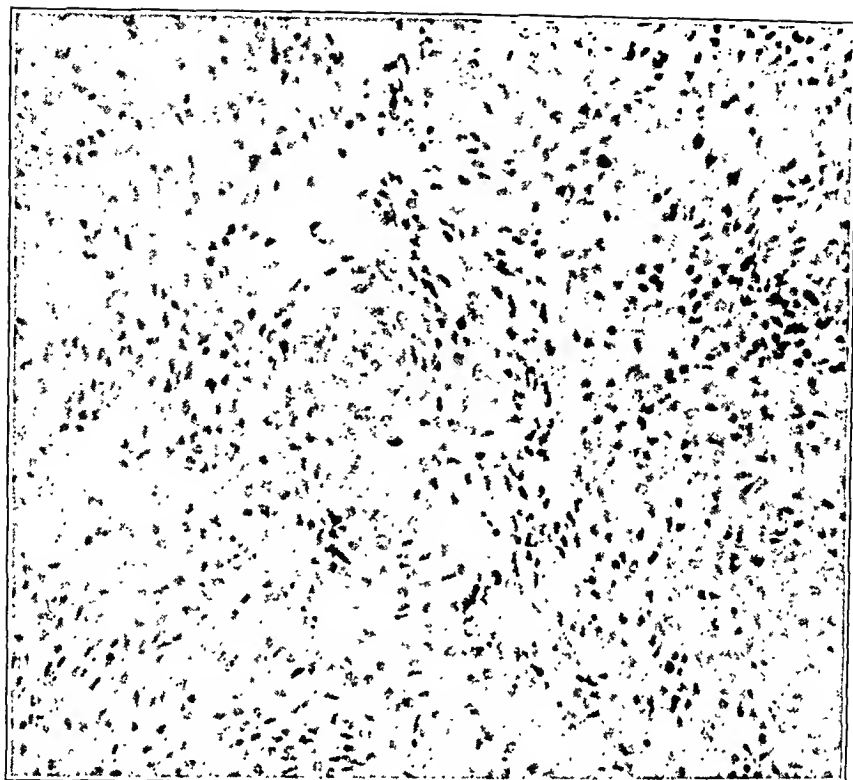


Fig. 8.—Section of the spleen of a dog before light ether anesthesia.

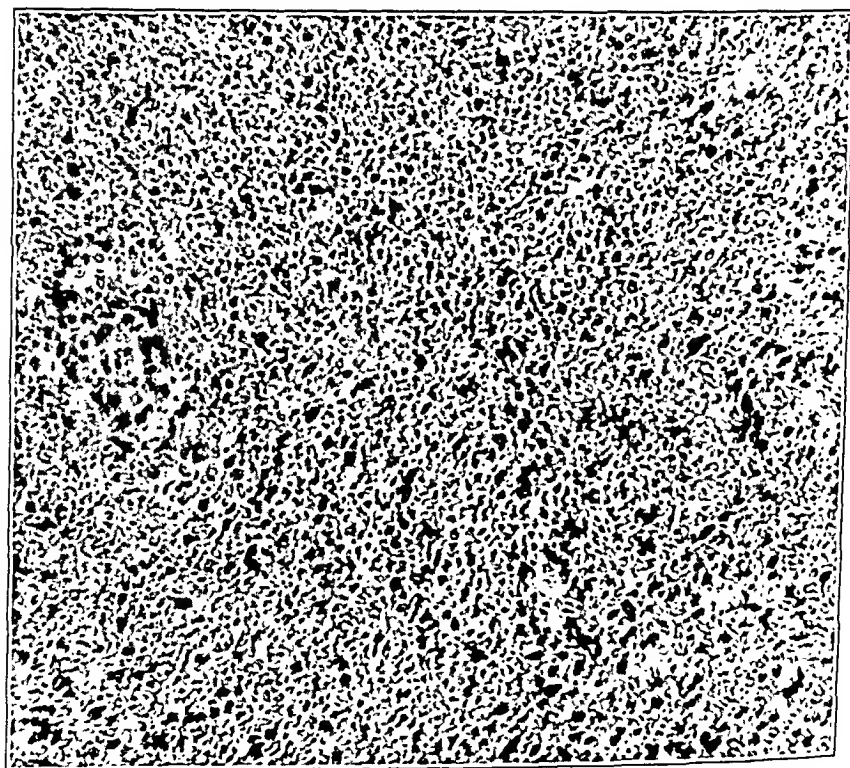


Fig. 9.—The same spleen after spinal anesthesia.

amount to the tissues; that is, there is tissue asphyxia. The venous blood, having come into oxygen equilibrium with the tissues, reflects this anoxia. The anoxia is also reflected in the tissue metabolism. Normally, glycogen is broken down into lactic acid, which is partly reconverted into glycogen and partly oxidized into carbon dioxide and water, both processes necessitating oxygen. Anoxia leads to an accumulation of lactic acid in the blood. As will be seen from the table, the low blood pressure is accompanied by such an increase in blood lactic acid. This result explains the finding of Saklad<sup>26</sup> of decreased carbon dioxide-combining power of the blood during spinal anesthesia.

In three control animals which were given morphine and ether in a similar way and 800 cc. of a 1 per cent solution of procaine hydro-

TABLE 6.—*Effect of the Hypotension of Spinal Anesthesia on the Arterial Oxygen Content*

Experiment No.	Time	Blood Pressure, Mg. of Hg	Arterial Oxygen, Volumes %	Venous Oxygen, Volumes %	Lactic Acid, Mg. per 100 Cc.
1	10:15	120	22.0	10.7	
	11:40	50 1 hr.	23.0	6.5	
	12:55	Above 80 1 hr.	....	15.8	
2	9:52	118	22.8	13.0	
	11:12	65 1 hr.	22.1	10.1	
3	9:55	115	15.8	12.5	
	10:03	Artificial respiration started			
	10:11	118	23.0	12.7	
	11:57	50 1 hr.	19.0	5.8	
4	10:01	108	21.0	16.8	35.0
	11:36	60 45 min.	22.0	7.4	45.0
5	10:16	128	21.8	20.0	28.5
	11:38	60 70 min.	21.7	10.0	45.0
	2:00	Above 80 105 min.	21.7	14.7	29.0
6	11:06	115	20.0	17.7	34.0
	1:55	40 1 hr.	19.6	9.5	84.0

chloride subcutaneously, there was a slight rise in the lactic acid content due to the light ether narcosis. This rise was fairly constant throughout and did not increase after the subcutaneous injection of procaine hydrochloride.

The reduction of cardiac output in spinal anesthesia found by Burch and Harrison,<sup>27</sup> the diminished ability to endure hemorrhage found by Burch, Harrison and Blalock<sup>28</sup> and the presence of stagnant anoxia found in this work are parts of the picture of what has been called

26. Saklad, M.: Studies in Spinal Anesthesia, Am. J. Surg. **11**:452-460 (March) 1931.

27. Burch, J., and Harrison, T. R.: The Effect of the Administration of Fluid on the Fall in Blood Pressure Caused by Spinal Anesthesia, Arch. Surg. **22**:1045-1046 (June) 1931.

28. Burch, J.; Harrison, T. R., and Blalock, A.: A Comparison of the Effects of Hemorrhage Under Ether Anesthesia and Under Spinal Anesthesia, Arch. Surg. **21**:693-697 (Oct.) 1930.

neurogenic shock. Labat<sup>29</sup> and Koster and Kasman<sup>2</sup> have taught that even if the blood pressure falls to such a low point as not to be measurable, the fall is harmless. Their basis for this belief is that in a large number of cases in which spinal anesthesia was used they have not had

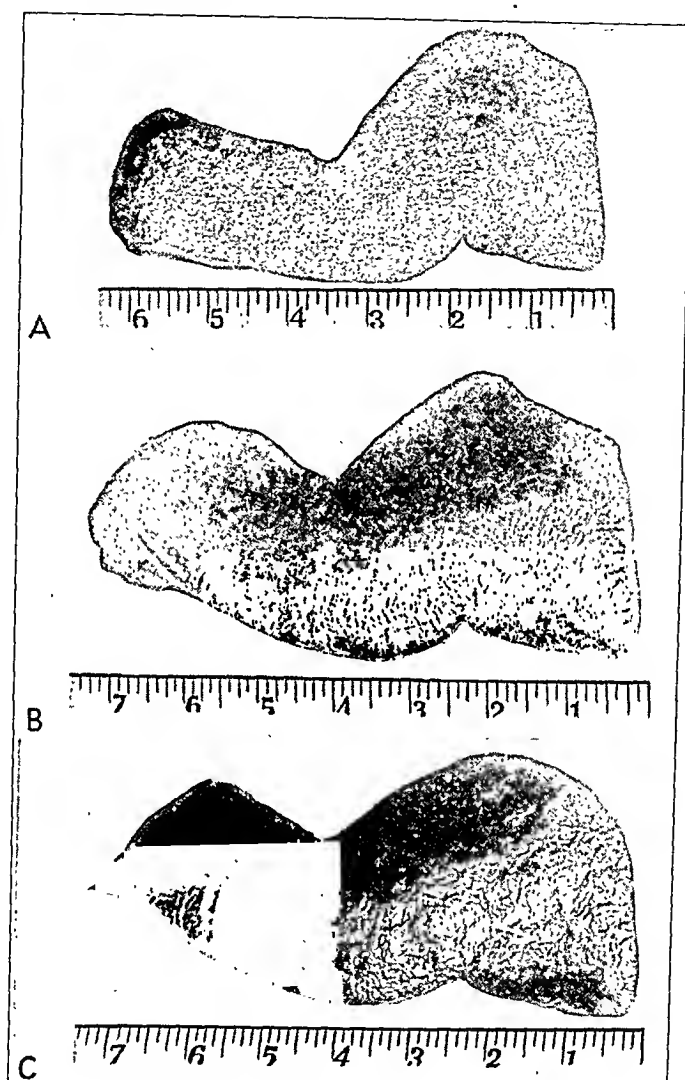


Fig. 10.—Three views of the spleen shown in figures 8 and 9. The dog was given premedication with morphine and chloralose. Procaine hydrochloride, 300 mg. in 3 cc. of water, was injected into the first lumbar space. In *A* there is some degree of splenic dilatation with the premedication; in *B* there is marked dilatation after spinal anesthesia, and in *C*, marked contraction of the spleen after the administration of ephedrine. In *B* note the marked curling at the upper margin and also the widening and thickening.

29. Labat, G.: *Regional Anesthesia*, Philadelphia, W. B. Saunders Company, 1924, p. 459.

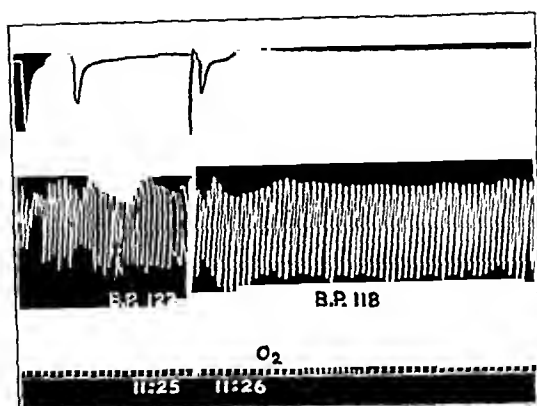


Fig. 11.—Tracing made on a dog weighing 12 Kg. that was given 5 mg. of morphine hydrochloride per kilogram of body weight subcutaneously, 70 mg. of chloralose per kilogram of body weight intravenously and tracheal irrigation of pure oxygen. Note the apnea and maintenance of the blood pressure.

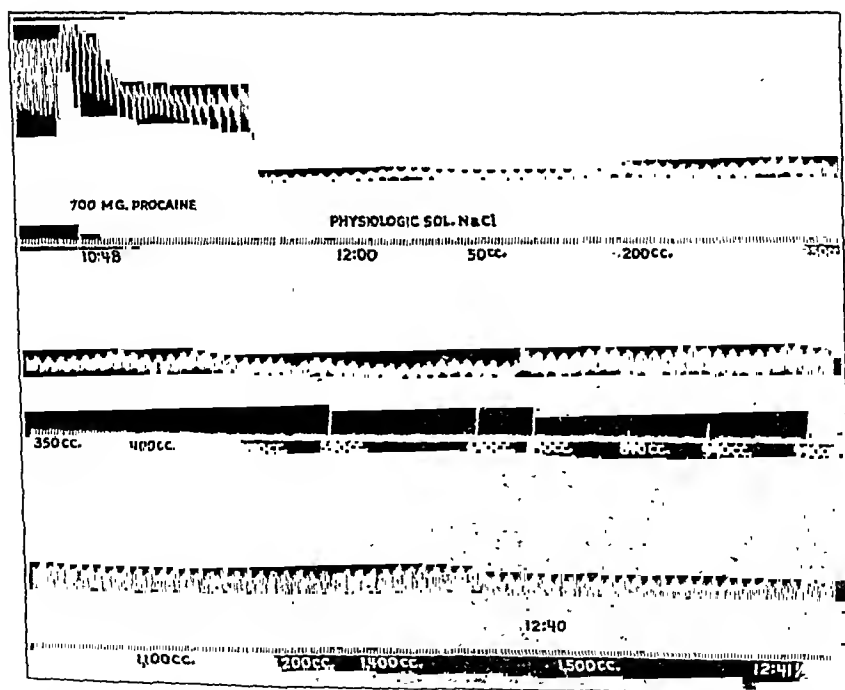


Fig. 12.—Tracing showing the effect of infusion of physiologic solution of sodium chloride in shock due to spinal anesthesia. The dog used weighed 19 Kg. and measured 87 cm. in spinal length. Dial and ethyl carbamate were used for narcosis. Note that infusion of even 1,500 cc. did not raise the level of the blood pressure.

a fatality. But death cannot be a valid criterion of whether or not harm is done, for the margin of safety in the animal organism is so wide that a great deal of injury can occur without producing death.

#### TREATMENT OF THE SHOCK DUE TO SPINAL ANESTHESIA

An effort was made to determine experimentally the comparative efficacy of the usual measures for combating shock due to spinal anesthesia, namely, the intravenous injection of saline solution, the transfusion of blood, the injection of ephedrine and the Trendelenburg position.

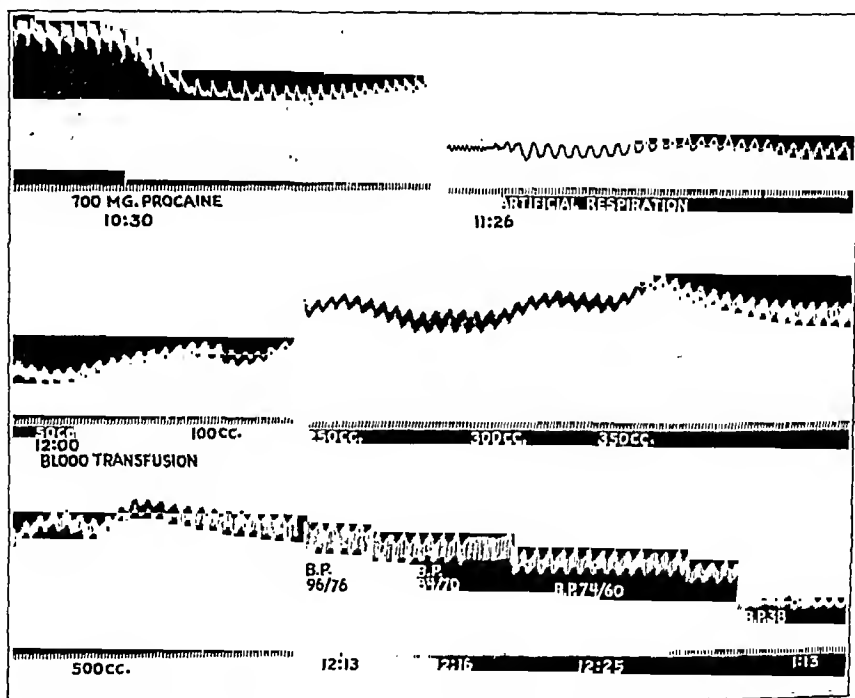


Fig. 13.—Tracing showing the effect of blood transfusion on an animal in shock due to spinal anesthesia. The dog used weighed 19 Kg. and measured 87 cm. in spinal length. At 10:05 5 mg. of morphine per Kg. of body weight was administered subcutaneously. At 10:20 ether was given and was discontinued at 10:27. In the strip made at 11:26 note that artificial respiration did not improve the blood pressure. In the strip made from 12:00 to 12:15 note that 500 cc. of blood, while raising the pressure during the injection, did not keep it from falling back to below shock level after the transfusion was discontinued.

In the experiment depicted in figure 12 physiologic solution of sodium chloride was injected into an animal in shock due to spinal anesthesia in quantities as large as the calculated total blood volume of the animal. This caused a transient rise in blood pressure, lasting as long as the infusion was continued, but soon

falling again to its previous level. In figure 13 it is shown that while blood transfusion causes a somewhat higher and longer rise, it is also inadequate.

The effect of ephedrine in this form of shock was studied in three sets of experiments. In a set of nine control experiments with spinal anesthesia it was found that in standard dogs from 700 to 800 mg. of procaine hydrochloride injected spinally caused a secondary fall so prolonged and profound that it required two hours or more after the blood pressure fell below 80 mm. to recover to 100 mm. It was also found in a series of six normal dogs used for timing the effect of ephedrine that a dose of 2 mg. of ephedrine hydrochloride per kilogram of body weight caused a rise lasting from forty-five minutes to one hour.

In the interval between the forty-five minutes to one hour and the two hours necessary for the recovery of blood pressure, there is over an hour in which to determine whether ephedrine actually improves the circulation or whether, like the infusion of physiologic solution of sodium chloride and of blood, it leaves the circulation without any material improvement after its effect is over.

In eight standard animals it was found that the intravenous injection of this dose of ephedrine hydrochloride within the first five to ten minutes after the blood pressure reached shock level caused the blood pressure to maintain its level of over 100 mm. from one and one-half to two hours after the injection of ephedrine, that is, until recovery. The tracings in figure 14 are representative for this experiment.

The reason for these results is obvious. The state of shock produced by spinal anesthesia is due primarily to the loss of nervous regulation of the peripheral circulation. To correct this by increasing the amount of fluid meets with two difficulties—the increase in the exudation of fluids into the tissue spaces and the great increase in the volume of the vascular bed. Ephedrine, however, because of its sympathetico-mimetic action, is a substitute for the lost nervous regulation and is therefore more effective. As may be seen from the spleen shown in figure 10 C, in which ephedrine produced contraction, and from figure 15, which shows a contraction of the posterior extremity in spinal anesthesia in response to ephedrine, this drug acts on organs affected by spinal anesthesia. This is to be expected as ephedrine, like epinephrine, acts on the so-called myoneural junctions of the sympathetic nerves distal to the point of the effect of spinal anesthesia.

Figure 16 shows the kymogram of a dog in shock due to spinal anesthesia. Fifteen minutes after the development of the shock, the dog was placed in the Trendelenburg position. The lowering of the head caused a rise of some 20 mm. of blood pressure lasting for less than a minute and falling again to the previous level. This is to be anticipated, as the raising of the distal part of the body drives the blood accumulating in the distal veins toward the heart, thereby increasing its output for the moment. But there is no lasting improvement in the circulation. The head-down position in other forms of shock is useful because this transient improvement causes an improvement in the



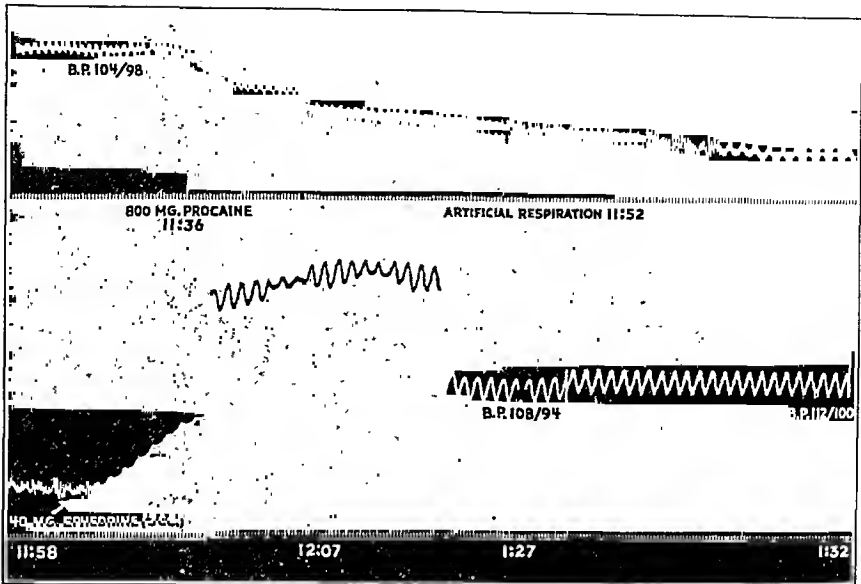


Fig. 14.—Tracing showing the efficacy of ephedrine if given early during shock due to spinal anesthesia. The dog used weighed 20 Kg. and measured 88 cm. in spinal length. At 11:02 5 mg. of morphine per kilogram of body weight was administered subcutaneously. At 11:25 ether was started and was discontinued at 11:32. At 11:58 2 mg. of ephedrine per kilogram of body weight was administered intravenously. At 12:07 the blood pressure was almost 200 mm. From 1:27 to 1:32 the blood pressure stayed over 100 mm., even after the effect of the ephedrine.

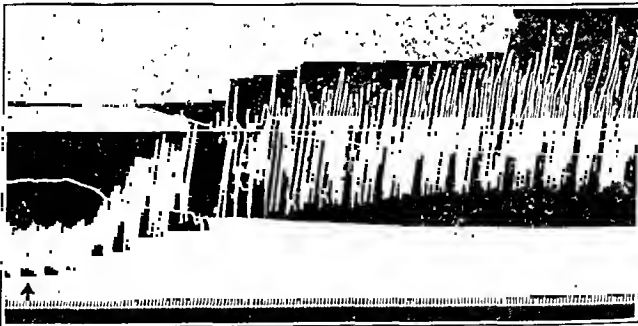


Fig. 15.—Same experiment as that shown in figure 3. The upper tracing shows the volume of blood in the hindlimb; the next tracing, the base line; the third tracing, the volume of blood in the foreleg, and the fourth, the blood pressure curve. The bottom tracing shows the time in seconds. At the time marked by the arrow, 1 mg. of ephedrine hydrochloride was injected intravenously. Note the decrease in the volume of both limbs and the rise in blood pressure.

medullary centers, which is reflected in an increased tone of the circulation, which, in turn, improves the centers further, thus breaking the vicious circle. But in order that this improvement may occur, the nerve pathway to the circulatory system, namely, the vasomotor nerves, must be intact. In spinal anesthesia these nerves are paralyzed, and the measure is therefore futile.

The danger of the Trendelenburg position when hyperbaric solutions are used is seen in the following three sets of experiments recorded in table 7.

The animals were all matched as to weight and spinal length. The drug was dissolved and made up to 3 cc. in distilled water and then injected into the first

TABLE 7.—*Effect of Trendelenburg Position*

Position	Weight, Kg.	Spinal Length, Cm.	Total Dose of Procaine Hydrochloride, Mg.	Specific Gravity of Solution at Room Temperature	Result
Horizontal	21	88	700	1.032	Survived
	20	88	700	.....	Survived
	19	88	700	.....	Survived
	19	87	800	1.039	Survived
	19	87	800	.....	Survived
	20	88	900	.....	Died in 26 min.
	21	88	900	.....	Died in 30 min.
	19	87	850	.....	Died in 35 min.
Head down 17°	19	87	600	1.029	Died in 17 min.
	20	87	500	1.026	Died in 15 min.
	20	88	400	1.018	Died in 16 min.
	21	88	400	.....	Died in 18 min.
	19	88	400	.....	Died in 20 min.
	19	88	350	1.016	Survived
	20	88	350	.....	Survived
	19	87	300	.....	Survived
Head up 17°	20	88	800	.....	Survived
	20	88	1,000	1.052	Survived
	20	88	1,000	.....	Survived
	20	88	900	.....	Survived
	21	88	900	.....	Died in 55 min.
	20	88	1,000	.....	Died in 50 min.
	21	89	1,000	.....	Died in 45 min.

lumbar interspace in from nine to ten seconds. In the first series the animals were kept in the horizontal position; in the second, they were in the head-down position at an angle of 17 degrees, and in the third, they were in the head-up position at the same angle. Each animal was anesthetized with 50 mg. of pentobarbital per kilogram of body weight intravenously, preliminary to the spinal injection.

The table shows that with the animal in the horizontal position it takes over 850 mg. of procaine hydrochloride to cause death in the animals by respiratory paralysis in an average time of thirty minutes. With the animal in the head-up position, from 900 to 1,000 mg. causes death in an average time of fifty minutes. When the head-down position was used, however, only 400 mg. was necessary to cause death in an average time of seventeen minutes. A recent paper by Grodinsky

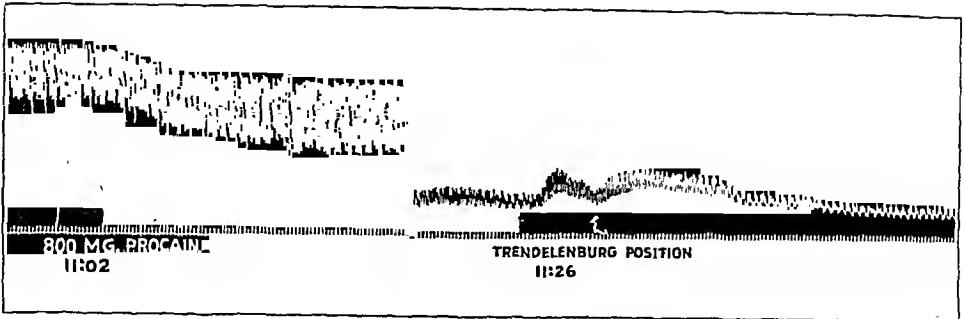


Fig. 16.—Tracing showing the effect of the Trendelenburg position on an animal in shock due to spinal anesthesia. The dog used weighed 20 Kg. and measured 88 cm. in spinal length. At 10:50 dial and ethyl carbamate were given intraperitoneally (50 mg. per kilogram of body weight). In the strip made at 11:02 note the slight primary fall. At 11:26 the Trendelenburg position was assumed in two stages (corresponding to the time marked by the two arrows). Note the slight rise and the gradual fall to a previous level or even lower.

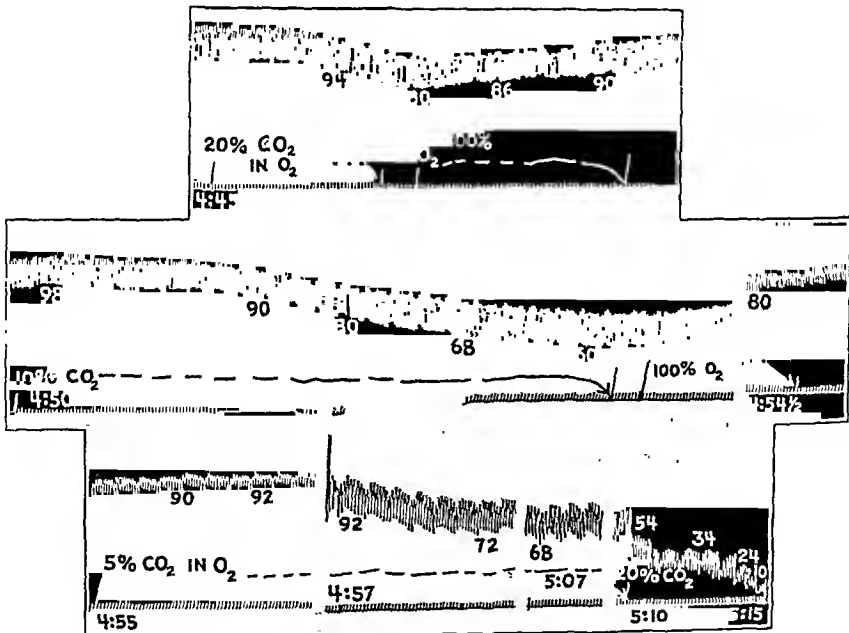


Fig. 17.—Tracings showing the effect of different concentrations of carbon dioxide and oxygen on the blood pressure. The dog used weighed 18 Kg. Morphine hydrochloride, 5 mg. per kilogram of body weight was administered subcutaneously and chloralose, 70 mg. per kilogram of body weight, intravenously. At 4:30 300 mg. of procaine hydrochloride was given intraspinaly. At 4:45 20 per cent of carbon dioxide in oxygen was given. Note the prompt fall of blood pressure and the rise again on inhalation of oxygen. At 4:50 10 per cent of carbon dioxide in oxygen was given. Note the longer latent period before the fall in blood pressure. At 4:54½ there is a gradual rise with 100 per cent oxygen. At 4:55 5 per cent of carbon dioxide in oxygen was administered. Note the still longer latent period. At 5:10 the animal was killed with 20 per cent carbon dioxide.

and Baker<sup>30</sup> showing that the head-down position of the cadaver caused a more cephalad spread of dyes injected into the spinal subarachnoid space lends support to this result. In all the dogs dying from respiratory paralysis, procaine hydrochloride was demonstrated qualitatively in the cisternal fluid after death. A study reported elsewhere<sup>31</sup> of the phenomenon of the gravitation current when a fluid of greater density is injected into one of lesser density and the system placed on an incline will aid in explaining why a larger lethal dose is required in the horizontal than in the head-down position. For, whereas a rapid flow to the medulla assures the arrival of the drug there in a relatively high concentration, a slow spread by molecular diffusion allows absorption, dilution, fixation and probably destruction.

#### THE USE OF CARBON DIOXIDE

Carbon dioxide has been misused as a respiratory or circulatory stimulant in spinal anesthesia. Heymans and his co-workers<sup>32</sup> have shown that it is contraindicated as it lowers the blood pressure further by its action on the peripheral vessels. CoTui, Rovenstine and McCloskey<sup>33</sup> have confirmed this and extended the study. Figure 17 shows the kymogram of a dog in spinal anesthesia under different concentrations of carbon dioxide and oxygen. The explanation of this seeming paradox is simple. When the sympathetic system is intact, the administration of carbon dioxide causes a centrally mediated general vasoconstriction, which raises the blood pressure. But when these nerves are paralyzed, the peripheral action predominates, causing vasodilatation and therefore a further lowering of blood pressure.

30. Grodinsky, M., and Baker, C. P.: *Spinal Anesthesia: A Clinical and Experimental Study*, Surg., Gynec. & Obst. **57**:187-205 (Aug.) 1933.

31. CoTui, F. W.: *Further Studies in Subarachnoid Anesthesia*, Anesth. & Analg. **13**:143-151 (July-Aug.); 183-192 (Sept.-Oct.) 1934.

32. Heymans, C.; Bouckaert, J. J., and Bert, P.: *Mécanisme du collapsus circulatoire: Influences des traumatismes et de la rachianesthésie sur les réflexes circulatoires sino-carotidiens*, Compt. rend. Soc. de biol. **112**: 714-716 (Feb. 24) 1933.

33. CoTui, Rovenstine and McCloskey: Unpublished results.

# CONGENITAL ABNORMAL ARTERIOVENOUS ANASTOMOSES OF THE EXTREMITIES

WITH SPECIAL REFERENCE TO DIAGNOSIS BY ARTERIOGRAPHY AND  
BY THE OXYGEN SATURATION TEST

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AND

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NEW ORLEANS

Arteriovenous fistula was first mentioned in the literature in 1757, when William Hunter<sup>1</sup> described the clinical features of the condition and the disturbed vascular physiology associated with it. In 1762 he reported the two cases, in both of which the condition was discovered by chance during phlebotomy, on which his description was based. A few years later Delacombe confirmed his observations at autopsy, and since that time a voluminous literature has grown up about the subject, most of which, however, concerns the traumatic or acquired variety.

The congenital variety has always been regarded as decidedly infrequent. Of four hundred and forty-seven cases reports of which were collected by Callander<sup>2</sup> in 1920 at the instigation of Halsted, only three fell into this category, and as late as 1930 Lewis<sup>3</sup> was able to find in the literature reports of only twenty-four cases, to which he added six of his own. Since surgeons have become conscious of the condition, however, the number of reported cases has decidedly increased. In 1928 Pemberton and Saint<sup>4</sup> reported nine cases observed at the Mayo Clinic in twelve years, but four years later Horton<sup>5</sup> was able to report from the same clinic twenty-four cases, in all of which involvement was limited to the extremities, observed in two years, which is another illustration of the fact that many supposedly rare conditions

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From the Departments of Surgery and Biochemistry of the School of Medicine of Louisiana State University, and from the Surgical Services of Charity Hospital in New Orleans.

1. Hunter, William, cited by Callander.<sup>2</sup>

2. Callander, C. L.: Study of Arteriovenous Fistula with an Analysis of Four Hundred and Forty-Seven Cases, *Johns Hopkins Hosp. Rep.* **19**:259-358, 1920.

3. Lewis, D.: Congenital Arteriovenous Fistulae, *Lancet* **2**:620-628 (Sept. 20); 680-686 (Sept. 27) 1930.

4. Pemberton, J. deJ., and Saint, J. H.: Congenital Arteriovenous Communications, *Surg., Gynec. & Obst.* **46**:470-483 (April) 1928.

5. Horton, B. T.: Hemihypertrophy of Extremities Associated with Congenital Arteriovenous Fistula, *J. A. M. A.* **98**:373-379 (Jan. 30) 1932.

become frequent if they are diligently sought for. In the last year we have observed seven cases, the reports of which are appended, and while we have made no effort to survey the literature, it seems reasonable to assume that a hundred or more cases are now on record.

The condition has been reported under a variety of terms, including arteriovenous fistula, abnormal pulsating venous aneurysm, arteriovenous varix, aneurysma serpentina, cirroid aneurysm, racemose aneurysm, hemihypertrophy, angiectatic hypertrophy, aneurysm by anastomosis, pulsating angioma and simple angioma. It seems to us that the term abnormal arteriovenous anastomosis is entirely inclusive and is less likely to give rise to confusion and misconception than any of the specialized terms listed.

#### DIAGNOSTIC CRITERIA

Before proceeding to the point of this paper, which is to report the seven cases personally observed and to emphasize certain diagnostic criteria employed in them, a few facts concerning congenital abnormal arteriovenous anastomoses may be briefly stated.

The condition is common to both sexes though perhaps it is slightly more frequent in males. It may develop or, more properly, may come to observation, at any age (as in the man 60 years old mentioned by Horton and the woman 71 years old observed by us), but it is more likely to attract attention in early life, particularly in childhood. The most common site of occurrence is the head and neck, and the next is the extremities, which was the site in all of Horton's and in our own cases. In contrast to traumatic abnormal communications, which are practically always single, the congenital type is practically always multiple, Reid's<sup>6</sup> case and one of our own seeming to be the only instances on record of single congenital arteriovenous communication.

The fundamental pathologic process, as Horton pointed out, is the same whatever the location, namely, a direct communication between the artery and the vein, without the intervention of the capillary bed, which is the normal channel of communication. The gross appearance, he stated, is best studied in the intracranial variety described by Dandy, in which the veins are free from accessory coverings and it is possible to see the pulsating red arterial blood flowing against a background of dark venous blood.

Obviously, the larger the fistula and the longer its duration, the more widespread will be the local pathologic process and the more marked the systemic reaction. Halsted, Matas, Reid, Holman and others have studied these pathologic changes in detail, and a rehearsal

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6. Reid, M. R.: Studies on Abnormal Arteriovenous Communications, Acquired and Congenital: I. Report of a Series of Cases, Arch. Surg. **10**:601-638 (March) 1925.

of their observations is not indicated in a communication of this purpose. It should be emphasized, however, for the point is constantly forgotten and the diagnosis is therefore many times missed, that abnormal communications between small vessels, even though they are multiple, are unlikely to produce the marked symptoms and the marked pathologic changes which even single communications between large vessels can bring about. When large vessels are involved, thrills and bruits are present, cardiac hypertrophy develops and ulcers are frequent, while spontaneous gangrene may be the end-result. When small vessels are involved, the veins in the course of years may become larger, elongated and tortuous, but thrills and bruits are likely to be absent, cardiac hypertrophy is not likely to develop and the most notable changes are likely to be the development of varicosities, ulcerations and perhaps hemihypertrophy.

The explanation of congenital arteriovenous communications, except in the briefest fashion, is again not relevant to this paper. The underlying principle, as stated by Sabin<sup>7</sup> and by Woollard<sup>8</sup> and based on their studies of the forelimb bud of the pig embryo, is that the common capillary plexus on which both arteries and veins develop is the basis for the persistence of a direct communication between the two systems. Both arteries and veins arise through differentiation from a common capillary plexus, and Sabin has shown that certain embryologic vessels may function as arteries at one stage of embryologic life and as veins at another, while Woollard has demonstrated the multitudinous communications present between the artery and the vein at the beginning of the process of differentiation. Rienhoff,<sup>9</sup> after personal observation of an experimentally developed fistula in the process of development, stated it as his personal view that the congenital type of abnormal vascular communication occurs as the result of persistence of the vessels or communications of the primary anlage, which, failing to develop into the normal definitive vascular tree, form anastomotic channels either directly or indirectly between otherwise normally developed arterial and venous trunks. The hundreds of such communications frequently noted, as in case 1 of our own series, seem to support this theory. Reid<sup>10</sup> is correct in his observation that in view of the common bed

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7. Sabin, F. R.: Origin and Development of the Primitive Vessels of the Chick and of the Pig, *Contrib. Embryol.* **6-7**:61, 1917-1918.

8. Woollard, H. H.: The Development of the Principal Arterial Stems in the Forelimb of the Pig, *Contrib. Embryol.*, **14**:139, 1922.

9. Rienhoff, W. F.: Congenital Arteriovenous Fistula, *Bull. Johns Hopkins Hosp.* **35**:271-284, 1924.

10. Reid, M. R.: Arteriovenous Communications, Acquired and Congenital: II. Origin and Nature of Arteriovenous Aneurysms, Cirroid Aneurysms, and Simple Angiomas, *Arch. Surg.* **10**:997-1009 (May) 1925.

of development of each side of the vascular tree and the enormous constructive as well as destructive changes necessary before the final pattern is reached, it is a marvel not that congenital abnormal communications occasionally occur but that they do not occur more often.

That the condition is not often considered as a diagnostic possibility, chiefly, we would say, because the available methods for diagnosis are not employed, is shown by the fact that of the twenty-three cases personally reported by Horton from the Mayo Clinic, in only one was the condition recognized prior to the patient's admission. Undoubtedly many cases have been overlooked in all clinics, while in others the disease has been diagnosed as varicose veins or ulcers, trophic ulcers, thrombophlebitis, arthritis—often an associated condition—elephantiasis or peripheral vascular disease, and treatment accordingly given. It is not sufficiently emphasized in textbooks and other communications that thrills and bruits, while pathognomonic of the condition when they are present, are absent in many, indeed we would say in most, cases, particularly when only small vessels are involved. They were present in only fifteen of the twenty-three cases reported by Horton and in only one of the seven reported by us, and Horton observed that it is no more sensible to wait for their development to diagnose this condition than it would be to wait for the development of an epigastric mass to make the diagnosis of gastric carcinoma.

The first principle of diagnosis is a careful history. We have made it a routine practice in our clinic for the treatment of varicose veins to question all patients closely concerning the onset of their varicosities, the location of the first noted and the possible etiologic factors involved. Cases of varicose veins which follow such diseases or states as thrombophlebitis, infections of various sorts, surgical incisions and repeated pregnancies rarely need further consideration from this standpoint. The group of cases, on the other hand, in which the varicosities present early in life, without obvious cause, in which they are unilateral and in unusual locations and in which they are associated with ulceration, arthritic changes and hemihypertrophy, need further consideration, though again only a small number of them will prove to be true abnormal arteriovenous communications.

The small number of cases which fall into this group should be studied in three ways: by gross comparative examination of specimens of blood from the normal and from the affected extremity, by the oxygen saturation test and by arteriography. It is interesting to observe that the last two methods of diagnosis as applied to arteriovenous fistula were first used at the Mayo Clinic, whence so much of value has emerged. The oxygen saturation test was first used by the



late G. E. Brown,<sup>11</sup> of that clinic, in 1927 and was extended to the deeper veins by Horton in 1932. Failure to use this modification, it might be noted, is responsible for the missing of the diagnosis in many cases in which study of superficial veins does not yield the desired information. The first arteriovenous fistula to be diagnosed by arteriographic methods was reported by Horton<sup>12</sup> in 1933 and was of traumatic origin. In May 1935 Horton and Ghormley<sup>13</sup> published a report of two cases of congenital origin in which the condition was diagnosed by the same method. Arteriography for arteriovenous fistula has also been used and reported by Yater and White.<sup>14</sup>

The first step in diagnosis is the withdrawal of specimens of blood from the veins of the normal and the affected extremities. As a rule, unless the abnormal anastomosis is very small and deep, the blood from the affected extremity is the usual bright red arterial blood, while that from the normal extremity is the normal dark blue venous blood. In one of our own cases (7) it was the accidental observation that the color of the blood from the right basilic vein was different from that from the left basilic vein which led to the discovery of the condition.

To Horton's and Brown's oxygen saturation test we have added another modification, the study of individual samples of blood withdrawn at various levels of the affected extremity, which is divided into segments by the use of tourniquets. This method reveals the exact location of the anastomosis and, further, is of decided value in those cases in which the anastomosis is not sufficiently extensive to change the character of the blood throughout the limb and in which the diagnosis may be missed because the specimen of blood is taken from an area too remote from it to be affected by it.

The patient is placed at rest, in the prone position and with the leg elevated, for a sufficiently long time for the blood to drain completely out of the veins. Then, while the leg is still elevated, tourniquets are applied, dividing it into as many segments as may be desired, after which the patient stands until the superficial veins and varicosities are filled with blood. At this time samples of blood are withdrawn from various levels and are compared with similar specimens from the normal extremity.

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11. Brown, cited by Horton.<sup>5</sup>

12. Horton, B. T.: Arteriovenous Fistula Involving the Common Femoral Artery Identified by Arteriography, *Am. J. M. Sc.* **187**:649-652 (May) 1934.

13. Horton, B. T., and Ghormley, R. K.: Congenital Arteriovenous Fistulae of the Extremities Visualized by Arteriography, *Surg., Gynec. & Obst.* **60**:978-983 (May) 1935.

14. Yater, W. M., and White, C. S.: Roentgenographic Demonstration of an Arteriovenous Aneurysm by Means of Thorotrast, *Am. J. M. Sc.* **186**:493-495 (Oct.) 1933.

In case 1 (fig. 1) of our own series the use of this method immediately revealed the widespread character of the abnormality, and case 2 (fig. 2) furnishes another excellent illustration of the variation of the oxygen saturation of the blood adjacent to and remote from the anastomosis. Before the tourniquets were applied, blood withdrawn from the popliteal vein showed an oxygen saturation of 52 per cent and blood from the varicosities an oxygen saturation of 55 per cent, which is not a notable difference. After ligation of the saphenous vein, and again without the tourniquets, the oxygen saturation of the popliteal blood

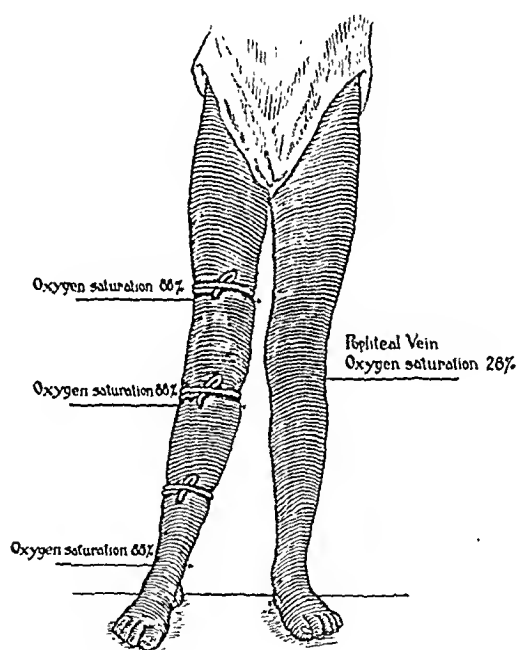


Fig. 1 (case 1).—Comparison of the oxygen saturation of the blood of the superficial veins of the extremity exhibiting hemihypertrophy with the oxygen saturation of the blood of the popliteal vein of the opposite normal extremity.

was 53 per cent, but in the varicosities it had increased to 77 per cent. Tourniquets were then placed at the middle third of the thigh and the upper and middle thirds of the leg, each segment thus being isolated, so that since there could be no backflow from above and no filling from below it necessarily filled only from its immediate tributaries. The oxygen saturation of the popliteal vein remained at 52 per cent, and the specimen from the lower segment showed the same percentage, but the specimen from the varicosity of the middle segment, where arteriography had already shown the abnormal anastomosis to be located, was now 84 per cent.

The samples of blood were collected under oil, and the oxygen contents and capacities were determined immediately according to the method of Peters and Van Slyke.<sup>15</sup> Since there is no set normal for the oxygen saturation of venous blood, the value of the test depends not on absolute standards but on a comparison of the oxygen saturation of blood from the vein studied with similar specimens from veins of the opposite extremity or veins at other levels of the same extremity.

By means of arteriography, as Horton pointed out in his original communication and as we have proved conclusively in the seven cases we have personally observed, it is now possible to locate the supposed

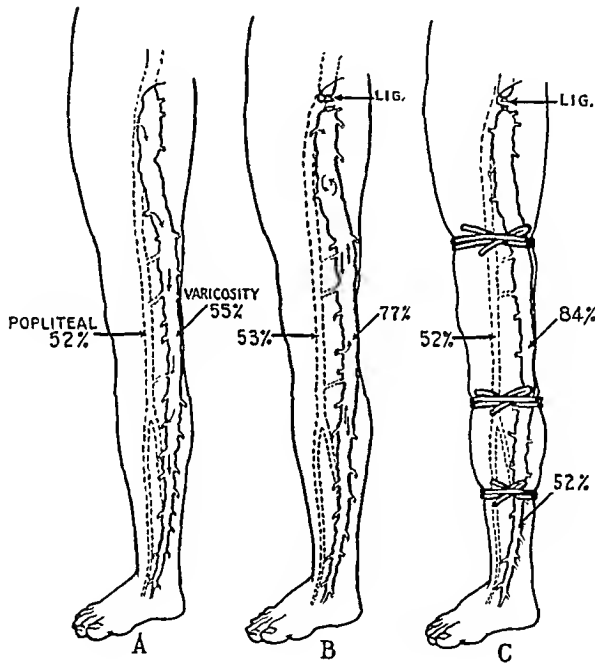


Fig. 2 (case 2).—Demonstration of the value of the tourniquet in the localization of the site of the abnormal anastomosis by means of the oxygen saturation test. *A* shows the percentage of oxygen saturation before ligation of the saphenous vein or application of the tourniquet; *B*, the percentage of oxygen saturation after ligation of the saphenous vein at the saphenofemoral junction, and *C*, the percentage of oxygen saturation after the application of tourniquets, showing that the abnormal arteriovenous anastomosis is located about the knee.

anastomosis with absolute accuracy as well as merely to confirm its existence. Injection of the vascular system with stabilized solution of colloidal thorium di-oxide as has been proved in the last three years and

15. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

in several hundred cases,<sup>16</sup> is a simple, efficacious, harmless method of demonstrating the state of the vascular tree, and in this type of pathologic change it is particularly valuable in that it demonstrates as no other method can the exact site of the abnormal communication, its size and the number and extent of the vessels involved.

The arteriograms, it should be emphasized, are not always easy to interpret. When the anastomosis is between large vessels there is naturally no difficulty. When smaller vessels are involved, however, repeated observations may be necessary, and it is essential that the plates be read by a person thoroughly conversant with the appearance of the normal vascular tree when it is visualized by this method, for only by comparison with normal standards can one detect abnormalities involving the small arteries and veins.

It would be highly improper, of course, to propose a classification based on only seven cases, but at that it is interesting to observe that in this small series certain definite types of anastomosis are noted, of which type *B* is the most frequent. The highly magnified schematic drawings which illustrate these various types (fig. 3) were made directly from the arteriograms of these patients and may be described as follows:

Type *A*. The normal distribution of the arterial system in the region of the knee. The terminations of the small arteries are to be noted particularly.

Type *B*. A multiple type of communication which we have chosen to designate as arteriolar-venous. It involves only the more superficially placed smaller vessels. It is not inconceivable, we suggest, that this type of anastomosis is akin to the vascular nevus or "port wine" birth mark which occurs on the surface of the skin, and we hope at some future date to be able to study the latter condition by arteriography and attempt to verify our surmise.

Type *C*. A combination of two types of abnormal arteriovenous anastomosis. In addition to the variety already described as type *B*, there is present also the single anastomosis between a large artery and a vein (*c*), usually seen in the traumatic variety of abnormal arteriovenous communication. The upward path of the vein and its communication with the large varicosity (*d*) should be noted.

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16. Veal, J. R., and McFetridge, E. M.: Technical Considerations in Arteriography of Extremities with Thorotrast, *Am. J. Roentgenol.* **32**:64-71 (July) 1934; Arteriography in Gangrene of Extremities by Use of Thorium Dioxide (Thorotrast): Study Based on Twenty-Seven Cases, *Ann. Surg.* **101**:766-775 (Feb.) 1935; Adequate Circulation in Extremities: Arteriography as Test for Determining Limits; Preliminary Report Based on Thirty Amputations, *J. A. M. A.* **104**:542-545 (Feb. 16) 1935.

Type *D*. A type of communication between a digital artery (*a*) normal in size, shape and distribution and normal veins (*b*) by way of small arterioles or vascular pockets which resemble small tumors. This type of communication, we suggest, may finally develop into the true angiomatous type.

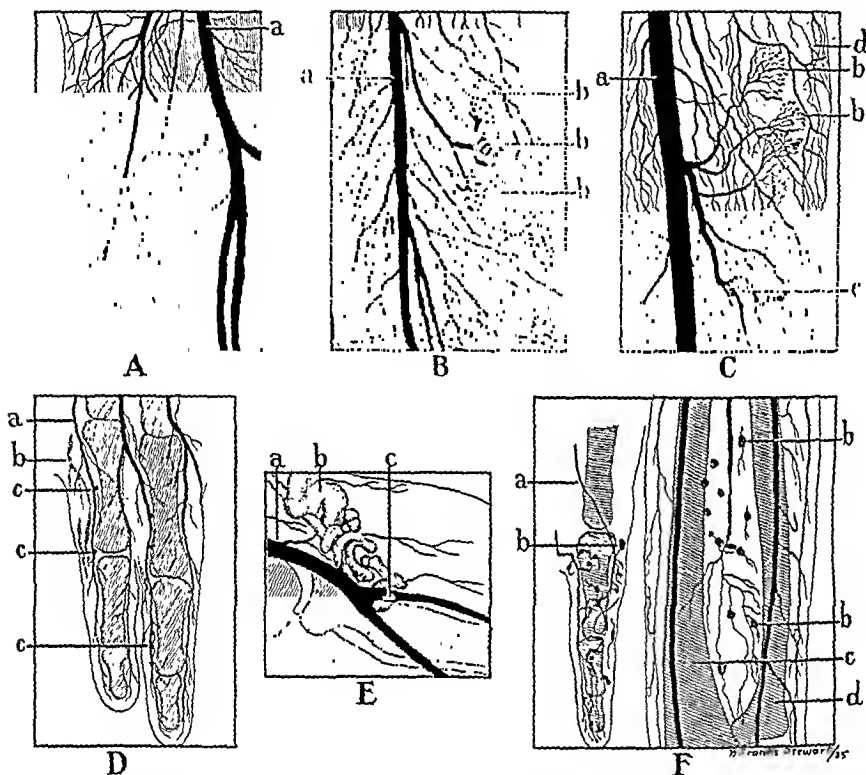


Fig. 3.—Schematic drawings made under magnification from arteriograms. *A* shows the normal distribution of the arterial system about the knee, *a* indicating the popliteal artery. Note the gradual branching and visualization of the fine arterioles. *B* shows an arteriovenous anastomosis just above the knee (case 1). The lower femoral artery is indicated by *a* and the dilated arterioles and small arteries at their terminations, just before entering the venous channels, by *b*. *C* shows an arteriovenous anastomosis which is a combination of two types (case 4). The femoral artery is indicated by *a*, dilatation of arterioles at their junction with the vein by *b* and single anastomoses between a large artery and a vein by *c*. Note that this vein also empties into the large varicosity shown in *d*, which is an example of the direct emptying of all the anastomoses into the large superficial varicosity. *D* shows an angiomatous type of anastomosis (case 7). Note the normal size and distribution of the digital vessels and the small vascular tumors through which the arteries empty directly into the venous circulation without an intervening capillary circulation. *E* shows a large single anastomosis between a vein and an artery just distal to the origin of the radial artery (case 3). *F* shows a section from an arteriogram of the lower part of the forearm and little finger (case 5) which demonstrates the formation of tufts of small arteries from arterioles. Note the direct communication between these arterial tufts and the venous circulation, without the intervention of a capillary circulation.

Type *E*. A direct single communication between a large artery and vein (*c*) arising in dilated varicosities. This type of anastomosis, as has been pointed out, is the type usually seen in the acquired form but is not usual in the congenital form. The proximal dilatation of the artery, to which Halsted was the first to call attention, is well shown here in the radial artery.

Type *F*. The angiomatous, or vascular tumor, type of communication. The digital artery (*a*) gives rise to numerous tufts of small arterioles which form vascular tumors. The same type of communication is noted throughout the lower half of the forearm.

In the seven cases, then, there are five distinct types of abnormal arteriovenous communication, three cases (1, 2 and 6) being instances of the arteriolar-venous, or *B*, type and the same type of anastomosis also appearing in association with another variety in case 4. Clearly this is the most usual type. It will be of interest to study additional cases, however, according to this classification, to determine whether the other types seen in this small group are accidental departures from a standard pattern or actually represent other varieties of anastomosis.

#### TREATMENT

The treatment of traumatic or acquired arteriovenous fistula is usually a fairly simple matter, since the communication is usually single and, as Pemberton pointed out, involves large vessels accessible to surgical approach; the problem, therefore, is limited to checking the arterial leak without interference with the blood supply of the tissues, and the abundant collateral circulation usually obliterates the risk of gangrene. The treatment of congenital abnormal communications, however, is another matter, since the connecting channels are practically always multiple and are frequently so small that direct surgical attack is difficult if not impossible. The ideal treatment, extirpation of the offending anastomosis, for obvious reasons is rarely possible. Ligation of the artery alone does little good in most cases and may do considerable harm. In seven of the thirty-four cases reported by Lewis, for instance, ligation of the artery had to be followed by amputation because of the development of gangrene. There is less risk if the vein is ligated also, but as a rule ligation proximal to the fistula serves merely to diminish the amount of blood flowing through it, the proportionate distribution being little changed and the diminished flow actually being detrimental, if anything.

The value of arteriography as a method of determining therapy in arteriovenous fistulas was pointed out by Horton in his first report, and we have found it of great value, especially in combination with the Perthes test of the deep circulation. Horton also mentioned its value

as a posttherapeutic measure, to check what has been achieved by the treatment adopted.

In our own cases, for instance, we were able to determine that in case 3, in which the communication was apparently single (fig. 4), simple ligation of the anastomosis would be sufficient, and we regret that the patient's refusal to consider surgical treatment made the test of our position impossible. In case 1 the widespread character of the anastomoses, as demonstrated by arteriography, showed that any surgical measure short of amputation, which was not then indicated, would be useless. In cases 1, 4 and 6, in which arteriography demonstrated



Fig. 4 (case 3).—Arteriogram showing an arteriovenous fistula arising from the radial artery. Note the single communication and the tortuous and dilated veins.

the superficial character of the anastomoses and the Perthes test showed the deep circulation to be adequate, the use of sclerosing substances seemed as safe as it proved to be.

In case 5, that of the angioma of the hand and forearm, arteriography (fig. 5) showed that the sclerosing substance could not possibly reach all the involved vessels, and the surgeon in charge of the case thereupon decided on amputation on the basis that a process of this sort is progressive and, in a sense, malignant. It is regrettable that circumstances make amputation the only possible procedure in many

cases, which makes it conservative, as Pemberton and Saint pointed out, to be radical in early life and to treat abnormal vascular communications as soon as they are discovered, to avoid such consequences later. At what time amputation should be done, they added, in those cases in which it is necessary, depends on the patient, the site of the anastomosis, the rapidity of its development, the degree of local disability and the presence or absence of systemic changes. In the absence of cardiac changes or destruction of tissue it may be safely deferred, they concluded, until inconvenience and disability demand it.

Surgical treatment is not always a simple matter in such cases. Busche, whose case Callander cited, removed a purple, pulsating tumor

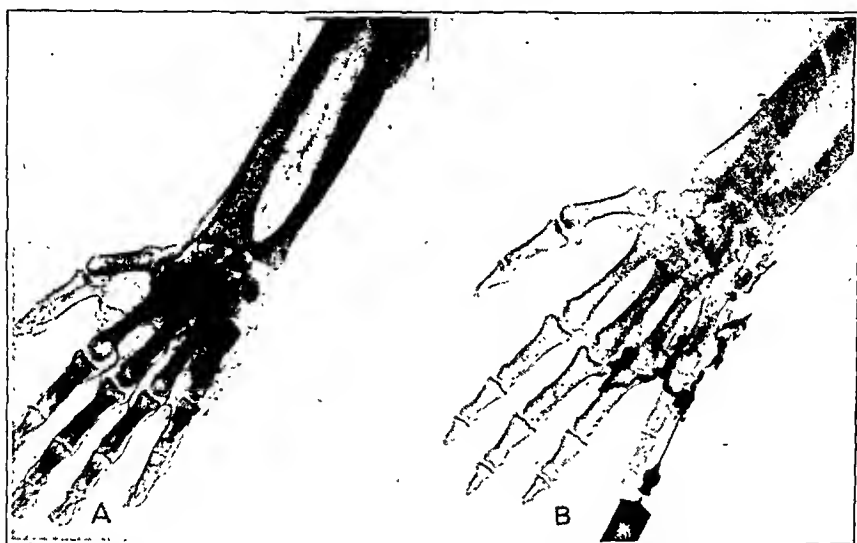


Fig. 5 (case 5).—*A*, an arteriogram of the lower part of the forearm and hand, showing the distribution of the hemangiomas. *B*, visualization of the venous tree after the injection of a stabilized solution of colloidal thorium di-oxide. Note that the angiomatous tumors fill from the venous as well as from the arterial side.

of the right temple in a young child "with a few quickly executed sweeps of the scalpel." But cauterization of the wound and finally ligation of the external carotid artery were necessary to control the hemorrhage which persisted from the whole raw surface. Bernheim<sup>17</sup> reported another case of arteriovenous fistula of the first part of the brachial artery and vein in which amputation, prepared for with the utmost care, was followed by a terrific, exsanguinating, almost fatal, hemorrhage.

17. Bernheim, B. M.: Congenital Arteriovenous Fistula in Left Brachial Artery and Vein with Secondary Arterial Blood Supply to Arm, *Ann. Surg.* **81**: 465-469 (Feb.) 1925.



The number of cases in which treatment was obviously needed but was not given, probably because the choice seemed to lie between no treatment and amputation, is as surprising in the reported series as is the paucity of reported cures. The three patients in our own small series who were treated by the simple injection of a sclerosing substance, in one case after ligation of the saphenous vein, have remained well to date, though it is too early, of course, to say that the cure will be permanent.

#### REPORT OF CASES

CASE 1.—A Negro girl aged 13 first observed at 6 years of age that her right leg was longer and larger than her left (fig. 6). Undoubtedly her attention was attracted to the abnormality by the fact that at the same time a dull, aching pain



Fig. 6 (case 1).—Hemihypertrophy and superficial varicosities. Note the uniform enlargement of the involved extremity and the absence of any trophic disturbance.

developed in the same leg, which was more severe in the knee and foot, which had persisted since and which was aggravated in the muscles of the calf by full extension of the extremity. Her history was otherwise without incident.

Except for this condition and an associated enlargement of the right labium majus, the physical examination gave essentially negative results. The right labium majus was almost twice the size of the left but exhibited no dilated vessels or other abnormalities which might account for the enlargement. The child had a typical scoliosis and walked with a definite limp. The right saphenous vein was grossly enlarged, but no trophic disturbances were present and no edema. There was no thrill or bruit at any level. From the anterior superior spine of the

ilium to the tip of the internal malleolus the right leg measured 79 cm. and the left 74.5 cm. From the anterior superior spine of the ilium to the tip of the patella the right leg measured 39 cm. and the left 37 cm. The circumference of the right leg was from 1 to 2 cm. larger than the left, depending on the level at which the measurements were taken, and the toes on that side were slightly (0.25 cm.) longer than the toes on the left foot.

The Wassermann reaction was negative. The blood count showed marked secondary anemia (3,630,000 red cells with a hemoglobin content of 80 per cent). The blood chemistry was within the normal range, and the basal metabolic rate was minus 9. A flat plate of the heart, supplemented by electrocardiographic study, revealed no abnormalities. Roentgenographic study of both extremities showed the bones of the right leg to be uniformly longer and larger than those of the left.

Tourniquets were applied to the right leg above the knee, at the middle of the leg and about the ankle, and specimens of blood were secured from each of the three segments. All of them were bright red, in contrast to the bluish blood from the left popliteal vein, from which it was secured in the absence of dilated superficial veins. The specimen from the left leg showed an oxygen saturation of 28 per cent against 86 per cent for the specimen from the right thigh and 88 per cent for the specimens from the middle of the leg and the lower segment.

The absence of bruits and thrills suggested that if an abnormal arteriovenous communication should be present, as the hemihypertrophy would seem to indicate, only small vessels were involved. The uniformly high oxygen saturation again suggested that the anastomoses were probably multiple and probably involved the entire leg. Arteriography with a stabilized solution of colloidal thorium di-oxide confirmed both these surmises. Although the femoral and popliteal arteries and the larger superficial branches were entirely normal, the smaller, more superficial arteries were markedly dilated. Furthermore, throughout the entire area visualized, namely, from the lower half of the thigh to the foot, these vessels emptied directly into the venous channels, literally by the hundreds. A second exposure, ten seconds later, revealed what is best described as a sort of snowbank mottling of the opaque material throughout the entire leg and the lower part of the thigh.

These findings are in direct contrast to the findings in normal persons. When the vascular supply is normal, an arteriogram taken immediately after the injection of the opaque substance shows it filling not only the larger arteries but also the small arterial vessels, in which it apparently terminates. A second picture, made from six to ten seconds later, shows it in the veins, large and small alike, including the popliteal vein. Both the course and the contour of the vascular tree are smooth and even, and the distribution is according to a more or less definite pattern.

In this case there were multiple abnormal anastomoses between the arterioles and the venules of the involved extremity (type B), none of the larger or medium-sized arteries being affected but all of the smaller vessels, both superficial and deep, taking part in the anomaly. Some anomaly of the popliteal vein was apparently present also, for it was not visualized, nor could it be located with the exploring needle.

Because of the widespread character of the anastomosis, plus the fact that the patient's pain was markedly increased when she was made to walk with the tourniquets in place, it was felt that injection of some sclerosing substance into the superficial veins was contraindicated and would, in addition, be of no value. Indeed, the character of the anastomosis seemed to preclude any treatment for the

present, though amputation may be necessary later. The child was accordingly discharged, after intensive treatment of the secondary anemia, with instructions to return at regular intervals for observation.

CASE 2.—A white man aged 36 applied to the Charity Hospital for the treatment of large varicosities of the lower part of the right thigh and the upper part of the leg. They had been noted for the first time about the twentieth year of life and had gradually increased in size. Pain had been associated with them for a number of years and recently had been so severe that the patient was almost incapacitated. The extremities were equal in size and length, and no trophic disturbances were noted. Perthes' test of the deep circulation gave negative results. No bruit or thrill was present in the standing position, but the early onset, the large size and the unilateral character of the varicosities suggested the diagnosis of an abnormal arteriovenous communication, and the patient was therefore studied from this standpoint.

Arteriography showed a normal circulation in the lower two thirds of the right leg. In the upper third of the leg and the lower third of the thigh were noted frequent abnormal communications between the smaller arteries and the varicosities described, the anomalous channels being considerably more numerous just above the knee (type *B*).

The oxygen saturation test, without the use of tourniquets, showed an oxygen saturation of 52 per cent in the blood from the right popliteal vein and of 55 per cent in blood from the varicosities at the level of the right knee. After ligation of the saphenous vein at the saphenofemoral junction, the oxygen saturation of the blood from the varicosities was 77 per cent and of the blood from the popliteal vein, 53 per cent. When tourniquets were applied at the middle of the leg and just above the knee, there was no change in the oxygen saturation of the popliteal vein, and blood from the lower segment of the leg, at the ankle, showed almost the same percentage, 55 per cent, but blood from the thigh, between the upper and the middle tourniquets, showed oxygen saturation of 84 per cent, which proved conclusively that the abnormal anastomosis involved only this area.

Under treatment with repeated injections of sodium morrhuate there was prompt thrombosis of the varicosities, and the patient was relieved from his symptoms. He has remained well for nine months, and repeated examination of the involved area has shown no tendency to recurrence of the varicosities.

CASE 3.—A Negro man aged 32 was admitted to the Charity Hospital for the treatment of gastro-enteritis. In the course of routine examination large varicosities were noted in the left antecubital space. Careful questioning revealed the fact that they had existed since early childhood, perhaps from birth, and had gradually increased in size. There was no difference in the size or length of the arms, and the patient, who was a laborer, had observed no weakness or other abnormality of the affected arm.

The radial pulse was the same in the two arms, as was the blood pressure above the elbow, and no trophic disturbances were noted. Roentgenographic study showed no changes in the bones. A distinct thrill could be felt over the varicosities on palpation, and a loud bruit was noted on auscultation, which disappeared when the brachial artery was compressed.

The oxygen saturation of blood from the left antecubital space was 81 per cent, against 21 per cent for a similar specimen from the right arm. Arteriography (fig. 4) showed a single large, direct communication between the upper end of the radial artery and the superficial varicosities in the antecubital space (type *E*), and repeated study failed to reveal any other.

Undoubtedly the trouble could have been corrected by simple ligation of the vein involved, with excision of the varicosities, but the patient, in the absence of more annoying symptoms, refused treatment. Perhaps, too, operation would not have been as simple as it seemed, for in the similar case reported by Reid, which seems to be the only other one on record of a single congenital anastomosis, two operations were necessary and ten ligatures had to be applied on the various vessels directly or indirectly involved.

CASE 4.—A white woman aged 71, who was admitted to the hospital with a diagnosis of sciatica, complained of pain extending from the posterior aspect of the left thigh to the foot. It had been present for eleven years and was aggravated by standing and walking. The only point of interest in the physical examination was the presence of large varicosities extending from the left buttocks down to the posterior aspect of the thigh, where they united with the saphenous vein and continued down to the foot. They were first noted on the posterior aspect of the upper part of the thigh when the patient was about 18 years of age and had gradually increased in size and extent. Pain had developed eleven years before admission to the hospital. The early onset of the varicosities in such an unusual location naturally suggested the diagnosis of an abnormal arteriovenous anastomosis, and the patient was therefore studied from this standpoint.

Tourniquets were applied according to the method described, and blood was drawn at various levels. The specimens taken from the two segments above the knee were bright red, and those from the segments below the knee were typical dark venous blood.

Arteriography revealed many fine direct communications between the small arteries of the thigh and the varicosities described, with one direct anastomosis between a large muscular artery and a vein near the middle of the thigh, the vein becoming progressively larger and more dilated as it approached the varicosities. Beyond the anastomosis the vein turned upward and outward, emptying into the varicosities at the area in which the small abnormal anastomoses were located. This type of abnormal communication (*C*) actually is a combination of two other types, one between a large artery and vein (*E*) and the other between the arterioles and the venules near the skin (*B*). As far as could be judged from the single plate, all the dilated veins which were part of the abnormal anastomosis terminated in the upper 4 inches (10 cm.) of the varicosities.

The patient was treated by ligation (in two places) of the varicose veins, followed by repeated injections of sodium morrhuate. Satisfactory thrombosis followed, and the pain rapidly disappeared.

CASE 5.—A white man aged 24 was admitted to the service of Dr. Isidore Cohn in the Charity Hospital. Dr. Cohn requested us to make arteriographic studies, and the case is reported by his permission.

The patient complained of a dull aching pain in the middle third of the right forearm, which had developed fifteen days before admission and which was associated with a swelling of the forearm and hand. He stated that as long as he could remember small tumors composed of dilated veins had been present in this hand and arm. Physical examination revealed the masses described, which decreased in size when the extremity was elevated. Large, dilated veins coursed over the lateral posterior portion of the lower part of the forearm and the upper third of the hand, and bluish purple areas were observed on the palmar surface of the hand in the hypothenar region. The blood pressure was 100 systolic and 70 diastolic in each arm. There was no evidence of increased heat in the hand

and arm, and no trophic disturbances were present. The upper extremities were alike in size, length and function.

A flat plate of the right forearm and hand revealed atrophic changes in the fourth and fifth metacarpal bones and in the bones of the little finger. Thickening and induration of the soft tissues of the hypothenar region were also noted. Arteriography (fig. 5) with a stabilized solution of colloidal thorium di-oxide showed direct arteriovenous communication (type F) in many areas of the lower part of the forearm, the ulnar side of the hand and the small and ring fingers. The tiny arterioles were grouped in circular, tuftlike whirls, and the opaque substance passed rapidly from them into the veins. The interpretation of the arteriogram was that there were numerous vascular tumors along the lower part of the forearm and the ulnar side of the hand.

An unsuccessful attempt at ligation of the involved vessels was followed by amputation through the lower third of the humerus. The pathologist's report on the amputated specimen reads as follows:

On section there were seen numerous dilated and tortuous thin-walled vessels filled with blood clot, which were located in the extensor muscles, the digitorum longis muscle and similar structures. They extended down into the wrist, where they were located in the fascia and were closely adherent to the extensor tendons and terminated in the tip of the little finger. There was no involvement of the anterior surface of the forearm or hand. The diagnosis based on the microscopic picture was hemangioma.

CASE 6.—A Negro man aged 37 applied to the Charity Hospital for treatment of a large mass of tortuous and dilated varicosities located over the upper half of the posterior aspect of the right leg. They had first been observed at the age of 12 years and had gradually increased in size. The only symptom was a dull localized pain, which came on after the patient stood for a long time. There was no thrill or bruit, but when the limb was elevated the veins did not empty completely, as the usual type of varicose vein does.

The involved portion of the leg was divided into three segments by the application of tourniquets, and samples of blood were removed from each. All three specimens were bright red, and each showed oxygen saturation of approximately 90 per cent. Arteriography (fig. 7) showed multiple anastomoses between the arterioles and the venules (type B). Since the Perthes test of the deep circulation gave negative results, the use of injections of sodium morrhuate to produce sclerosis of the affected veins was considered safe, and under this treatment the patient has shown both objective and subjective improvement.

CASE 7.—A white man aged 23, a medical student, was undergoing routine tests when it was observed by one of us (W. M. McC.) that the blood withdrawn from his left basilic vein was unusually bright, whereas that from the right vein was the normal dark blue of venous blood. Examination showed the right arm to be slightly and uniformly larger than the left; there were no abnormalities of any sort in the left arm. There were no symptoms of any sort, and except for the accidental observation of the difference in the color of the blood from his arms, the condition would not have been discovered.

Examination of a specimen of blood from the left basilic vein, without the application of tourniquets, revealed the oxygen saturation to be 85 per cent, against 65 per cent for the specimen from the right side. Three arteriograms were made after the injection of a stabilized solution of colloid thorium di-oxide. The first exposure, made immediately after the injection, showed the opaque substance filling the arteries of the hand and the proximal half of each finger in

the normal manner. A second exposure, two seconds later, showed a completely changed picture. At this time all the digital arteries were visualized, and fifteen or twenty small dilated vessels were seen leading from the small arteries into the soft tissues. They were about the size of a pinhead, and their distribution was irregular; four or five were in the pulp of the thumb, and the others were located along the lateral margins of the finger. A third arteriogram, made six seconds after the second one, showed these dilated vascular pockets emptying directly into the venous circulation, with no evidence of a capillary circulation.

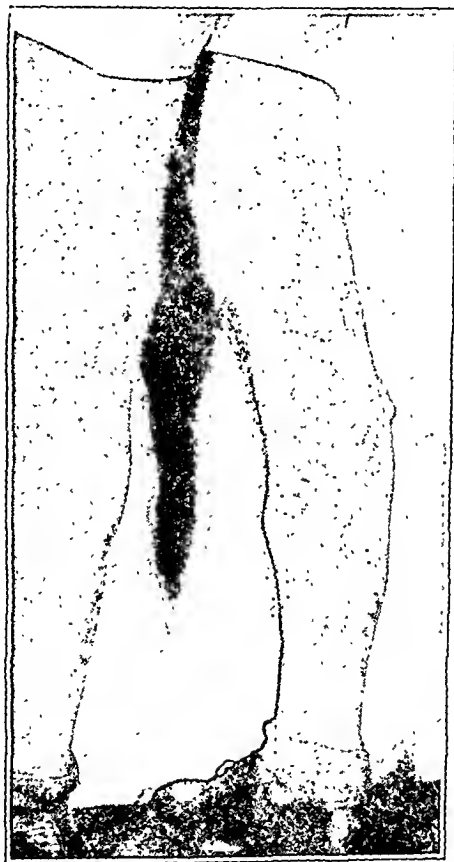


Fig. 7 (case 6).—Congenital arteriolar-venous anastomosis in the region of the right knee. Note the dilated, tortuous vessels and their distribution. The oxygen saturation of the venous blood from this region was 92 per cent, but no thrill or bruit was noted.

This type of anastomosis (*D*), while it is the most unusual of the whole series, undoubtedly is more frequent than is suspected, since it is probably, as in this case, discovered only by accident. This subject was not treated, in the absence of symptoms, and will probably never suffer from his abnormality, although he will be carefully followed to determine whether the condition is progressive. It may, of course, be an early manifestation of the hemangiomatous type of anastomosis (*F*).

## SUMMARY

Abnormal arteriovenous anastomoses of the extremities, especially small ones, are undoubtedly more common than is generally realized.

The congenital type, which has a true embryologic origin, on the basis of the derivation of each side of the vascular tree from a common bed, most often has multiple communications, in contrast to the usual single communication of the acquired type.

Such abnormal communications should be suspected in all cases of varicosities, particularly of the unilateral type, which appear early in life and in unusual locations. They should also be suspected in cases of chronic ulcers of the leg in young subjects without obvious cause, in cases of hemihypertrophy and in cases in which there are trophic disturbances of the extremity of obscure etiology.

The oxygen saturation test is an exceedingly useful diagnostic measure, the value of which is enhanced by the study of specimens of blood withdrawn between tourniquets, as suggested in this paper, which definitely locates the anastomosis by permitting the maximal concentration of arterial blood in the superficial veins.

The value of arteriography should also be emphasized, for there is no other method of demonstrating the exact site, type, number, size and distribution of the abnormal anastomoses.

A possible classification of abnormal anastomoses is suggested on the basis of the arteriographic findings in these few cases.

By use of arteriography it is possible to determine which patients should be treated by surgical measures, which can safely be treated by the injection of sclerosing substances if the Perthes test demonstrates the adequacy of the deep circulation and which must be left untreated unless and until amputation proves necessary.

Seven cases of congenital abnormal arteriovenous anastomoses are reported.

# CRANIAL VENOUS SINUSES

## CORRELATION BETWEEN SKULL MARKINGS AND ROENTGENOGRAMS OF THE OCCIPITAL BONE

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AND

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In a previous communication<sup>1</sup> one of us (B. W.) has described the normal anatomic variations in the cranial venous sinus patterns, particularly in the region of the torcular Herophili. As a part of that study, it was noted that the markings on the occipital bone closely corresponded to the differences in the volume of the lateral sinuses and followed exactly the distribution of these sinuses. To recapitulate, 47 of 100 roentgenograms of the skull showed equal markings, 32 demonstrated a noticeable difference in size, 15 showed indefinite markings on each side, 2 showed no bony evidence of the sinus pattern on either side and 4 showed no markings on one side and very definite markings on the opposite side. For practical purposes, discussed later, it is important to have a similar clinical record of these observations, and it is the purpose of this paper to correlate roentgenograms of this portion of the skull with the anatomic records already made.

Except for isolated instances, there are few reports in the literature pertaining to this subject. The most interesting of these is that of Ersner and Myers.<sup>2</sup> They discussed roentgenographic evidence secured in the course of the study of 4 cases of disease of the middle ear associated with thrombosis of the lateral sinus. The roentgenograms in the first case suggested absence of the right lateral sinus and dilation of the left lateral sinus, a finding that was substantiated at operation; those in the second case, one of sinus thrombosis involving the right side, revealed a larger left lateral sinus; those in the third case, one of sinus thrombosis on the right side, demonstrated a larger right lateral sinus; the roentgenogram in the fourth case, one of petrositis on the right

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From the Departments of Surgery and Roentgenology, Johns Hopkins Hospital.

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side, showed a larger left jugular foramen. Wanamaker<sup>3</sup> reported an instance of variation in the sinuses demonstrated roentgenographically; in this case the left lateral sinus was the smaller. Campbell<sup>4</sup> recommended the use of the roentgenogram to diagnose anatomic variations in the two lateral sinuses, but he did not pursue the subject in detail. Berg and Constans<sup>5</sup> studied the roentgenographic picture in 158 cases of mastoiditis prior to operation, paying particular attention to the location of the sinus plate in relation to the mastoid cells. In 11 cases the roentgenograms showed absence of the lateral sinus on one side; in 4 of these cases the absence was noted on the diseased side. Both Frenckner<sup>6</sup> and Dixon<sup>7</sup> have experimented with the injection of opaque mediums into the cranial venous sinus system, the former using monkeys and human cadavers and the latter dogs and in a few instances human clinical material. Their efforts, although highly laudable, have not as yet brought forth a controlled series of cases from which normal variations in the sinus pattern may be ascertained. Finally, Moniz and his associates<sup>8</sup> have endeavored to picture the venous drainage of the brain in the course of arterial encephalography. Their plates, taken in a lateral plane from four to fifteen seconds after the intracarotid injection of 15 cc. of colloidal thorium dioxide, present an effective understanding of the patency of the sinuses. No study, however, of the normal venous patterns has been made.

The literature describing the relationship between the volume of the sinuses and the markings on the skull has already been extensively reviewed and confirmed personally. Little has been added since the classic work of Le Double,<sup>9</sup> whose conclusions may be quoted with profit.

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8. Moniz, E.; Alves, A., and de Almeida, F.: La visibilité de sinus de la dure-mère, par l'épreuve encéphalographique, *Presse méd.* **40**:1499-1502, 1932.

9. Le Double, A.-F.: *Traité des variations des os du crâne de l'homme et de leur signification au point de vue de l'anthropologie zoologique*, Paris, Vigot Frères, 1903.

The study of the variations in the posterior venous sinuses of the dura mater is quite favorable to the thesis that the primitive venous system of the brain is bilateral and symmetrical in origin. The greatest part of the variations in these sinuses consist, in reality, in their bilateral nature, their separation by a septum, continuous or interrupted, and of a varying length (gun barrel sinus), and lastly by their early or late bifurcation. This said, it is easy to explain the variations in the markings on the internal surface of the occipital bone; they correspond to the volume of the venous sinuses that they contain. Is it not an accepted fact that every vessel of consequence is generally indicated by a groove on the inner surface of the skull?

This study was undertaken on the first 100 satisfactory roentgenograms available in the files of the department of roentgenology of the Johns Hopkins Hospital. The plates were made of 56 males and 44 females, of whom 90 were white and 10 Negroes. There were from 14 to 23 persons in each of the first five decades of life, with only a few in the later periods of life. No attempt was made to choose specific films from a clinical or anatomic standpoint, except to rule out those which showed operative or pathologic deformities affecting the region of study. The criterion of choice was fundamentally that of selecting diagnostic films from an average technical point of view.

Since the primary interest in this work was centered in the torcular Herophili and the transverse portions of the lateral sinuses, only anteroposterior roentgenograms of the occipital bone were eligible for study, and only those were used that projected the area of the inion above the orbital margins. Since bilateral comparison was essential, only true projections of the sagittal plane of the skull perpendicular to the film were acceptable.

The occipital view only was used in this study (Whitmore,<sup>10</sup> Hirsch,<sup>11</sup> Jerman<sup>12</sup> and Towne<sup>13</sup>). This was chosen for several specific reasons in addition to the obvious one already noted. The selection of the anteroposterior view rather than the lateral stereoscopic view for the study of the lateral sinuses lessens not only the factor of human error in estimating differences but also that of technical variations that are inevitable in the latter projection. The occipital view is relatively simple to obtain, and the postural requirements are applicable to nearly any patient. Finally, as long as the primary projection criteria are observed in choosing films for study, a relatively wide range of tube-skull-film angulation is apparently permissible.

10. Whitmore, W. H.: The Occipital View: Modified Technique, *Am. J. Roentgenol.* **31**:271-272, 1934.

11. Hirsch, I. S.: *The Principles and Practice of Roentgenological Technique.* New York, American X-Ray Publishing Company, 1920.

12. Jerman, E. O.: *Modern X-Ray Technique.* St. Paul, The Bruce Publishing Company, 1928.

13. Towne, E. B.: Erosion of the Petrous Bone by Acoustic Nerve Tumor. *Arch. Otolaryng.* **4**:515-519 (Dec.) 1926.

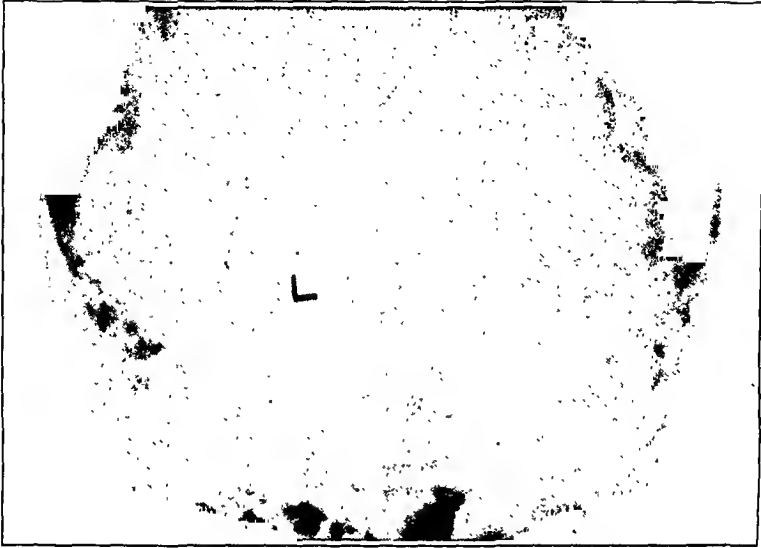


Fig. 1.—Anteroposterior roentgenogram showing lateral sinuses of equal volume.

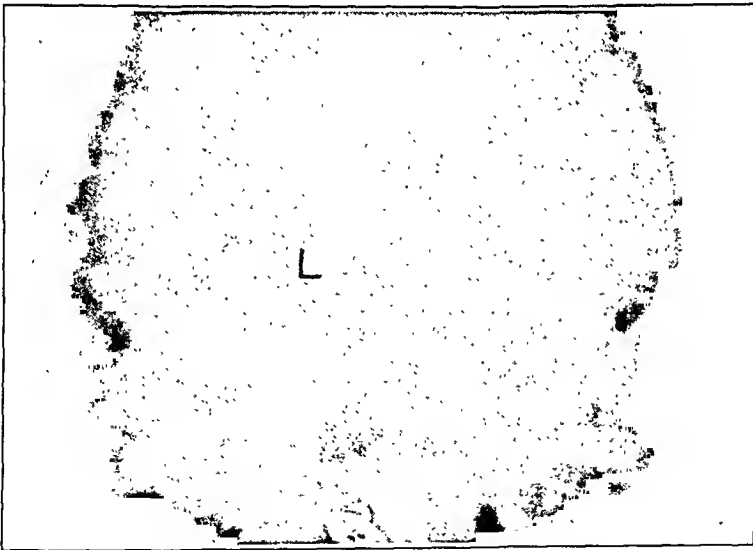


Fig. 2.—Anteroposterior roentgenogram of the lateral sinuses, the right being larger than the left.

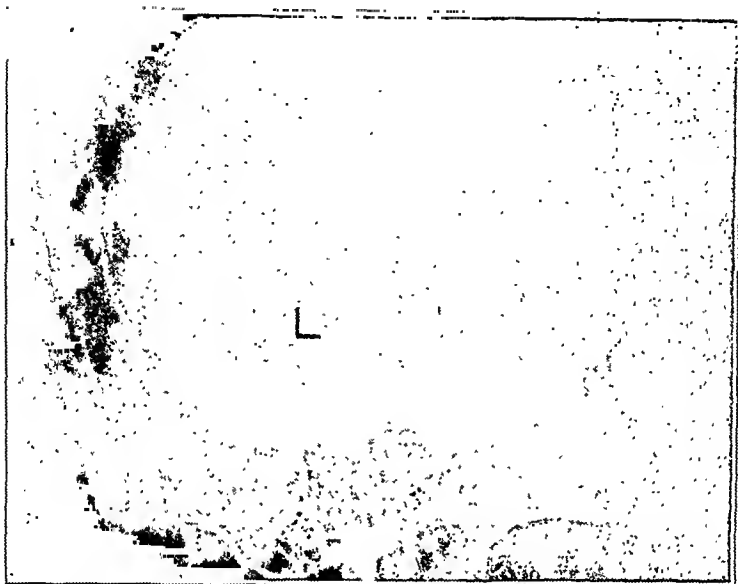


Fig. 3.—Anteroposterior roentgenogram of the lateral sinuses, the left being larger than the right.



Fig. 4.—Anteroposterior roentgenogram showing a right lateral sinus and absence of the left lateral sinus.



Fig. 5.—Anteroposterior roentgenogram showing a left lateral sinus and absence of the right lateral sinus.



Fig. 6.—Anteroposterior roentgenogram showing absence of bony markings of the lateral sinus.

On the other hand, relatively standardized technic in any roentgenographic examination is desirable, and the selections for demonstration were, of course, chosen from an optimum group. Since most optimum technics have eventually been ascertained by the trial and error method, after due theoretical consideration, it will take further study to evolve such a method for the evaluation of the relative caliber of the lateral sinuses. This problem will be considered in detail in a later report. For the present, the observations shown in tables 1 and 2 have been made.

TABLE 1.—*Variations in the Lateral Sinuses*

Sinuses	No. of Cases	Degree of Variation	No. of Cases
Bilateral and equal.....	46		
Right lateral sinus greater than left.....	30	Slight difference.....	8
		Moderate difference (2:1).....	15
		Pronounced difference (2:1 plus)	7
Left lateral sinus greater than right.....	11	Slight difference.....	1
		Moderate difference (2:1).....	5
		Pronounced difference (2:1 plus)	5
Indistinct markings .....	6		
Absence of markings.....	3		
Left lateral sinus present; no right.....	1		
Right lateral sinus present; no left.....	3		

TABLE 2.—*Comparative Anatomic Observations on Sinuses and Skull*<sup>1</sup>

Sinuses	No. of Cases	Degree of Variation	No. of Cases	Skull	No. of Cases
Bilateral and equal.....	48				47
Right lateral sinus greater than left	38	Slight difference.....	23		
		Moderate difference...	12		
		Pronounced difference	3	Noticeable difference....	32
Left lateral sinus greater than right	10	Slight difference.....	5		
		Moderate difference...	5		
Right lateral sinus present; no left	1			No markings on one side; marked on the opposite.....	4
Left lateral sinus present; no right	3			Indefinite markings.....	15

## COMMENT

Clinical evidence of the relative size of the lateral sinuses secured by the use of roentgenograms of the skull is of value from two points of view. It has long been established that the Queckenstedt test, or the application of the Queckenstedt test by Tobey and Ayer, is influenced by the caliber of the efferent cranial venous channels, i. e., the lateral sinuses and the jugular veins. A smaller channel, carrying a smaller volume of venous blood, will give a lower and slower response in the spinal manometer reading on compression of that channel and vice

versa. An advanced example of this anatomic abnormality in association with a positive Queckenstedt test has recently been noted.<sup>1</sup> Studies to demonstrate the correlation between the response to the Queckenstedt test and the roentgenographic evidence of the volume of the lateral sinus in normal persons are now under way to elucidate this problem. The observations in this paper, then, form the basis for further demonstration of the relationship of the volume of the sinuses, the markings on the skull, the roentgenographic evidence of these bony markings and the validity of the Queckenstedt test.

Secondly, in those cases of thrombosis of the lateral sinus or of the jugular vein in which there are signs of intracranial pressure without evidence of cerebral abscess, purulent meningitis, etc., it is of clinical value to appreciate the probable volume of the main venous channels leading from the brain. In three of Ersner and Myers' cases the larger venous channel was patent, there were no signs of increased intracranial pressure and the patients survived. In 1 case there was thrombosis of the larger sinus, as portrayed in the roentgenograms of the skull, and the patient died with evidence of advanced intracranial pressure. The authors stated:

In the cases that involved the side of the smaller sinus and jugular foramen, the pressure symptoms were practically nil, even those where X-ray revealed a suppuration of the petrous portion of the temporal bone. These symptoms were absent, due to adequate circulation. Those cases which involved the side of the larger sinus presented the neurologic signs which we recognize as being due to disturbances in venous circulation and to increased intracerebral pressure.

There are numerous other reports of back pressure phenomena in the brain, all, however, without roentgenographic evidence of sinus caliber. Those of Klestadt<sup>14</sup> Brinitzer,<sup>15</sup> Neubauer,<sup>16</sup> Cairns,<sup>17</sup> Ohnacker,<sup>18</sup> Uffenorde<sup>19</sup> and Syme<sup>20</sup> may be briefly noted.

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14. Klestadt, W.: Zerebrale Symptomenkomplexe bei otogener Sinusphlebitis, *Ztschr. f. Laryng., Rhin., Otol.* **13**:83-105, 1924.

15. Brinitzer: Hirnsymptome und Stauungspapille nach Sinusphlebitis, *Klin. Wchnschr.* **3**:1649, 1924.

16. Neubauer, A.: Nach acuter Mittelöhrrentzündung aufgetretene Sinus-thrombose mit Aphasie und Hemiplegie, *Jahrb. f. Kinderh.* **104**:361-364, 1934.

17. Cairns, Hugh: Abscess of the Brain, *J. Laryng. & Otol.* **45**:385-397, 1930.

18. Ohnacker, P.: Zirkulatorisch bedingte Hirnerscheinungen im Anschluss an Sinus- und Jugularisausschaltung, *Arch. f. Ohren-, Nasen- u. Kehlkopfh.* **131**: 1-12, 1932.

19. Uffenorde, W.: Zerebrale Symptome bei unkomplizierten otogen Extra-duralabszess und bei Sinus thrombose, *Ztschr. f. Laryng., Rhin., Otol.* **22**:151-159, 1932.

20. Syme, W. S.: Two Unusual Cases of Lateral Sinus Thrombosis, *J. Laryng. & Otol.* **48**:547-550, 1933.

## CONCLUSIONS

A preliminary study of 100 consecutive routine roentgenograms of the occipital bones of normal persons, taken in the anteroposterior projection plane, has demonstrated relative differences and variations in the size of the bony markings of the lateral sinuses that closely correspond to the anatomic observations previously reported.

This normal standard of variation, appraised by roentgenographic study, is of clinical value in determining the significance of irregularities obtained by the Queckenstedt test and in determining the dynamics of the venous return from the brain in the presence of thrombosis of the lateral sinus or of the jugular vein.

NOTE.—The photographs presented in this paper depict anteroposterior roentgenograms of the various sinus patterns. The particular films were chosen because they offered the most favorable chance for satisfactory reproduction. Any film in this large group, however, revealed its particular type of pattern satisfactorily; not all would reproduce convincingly.



# PREPARATION OF OPERATIVE FIELD

REPORT OF A SURVEY OF SEVENTEEN SURGICAL TEACHING CLINICS

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Resting with a false sense of security on the generally accepted listerian principle, the casual surgeon has not greatly concerned himself with advances in the preparation of the operative field. A large number of surgeons working in open hospitals accept this preparation as a matter of routine. The same unaltered technic may be in vogue many years without revision, until some accident, some grave infection of the wound or even a fatality will call attention to a fault in the technic. Recently Meleney,<sup>1</sup> from the service of the Presbyterian Hospital in New York, surveyed the cases of infection of the wound over a period of ten years and found that 12.5 per cent of the clean wounds showed some type of inflammatory reaction. In a recent symposium from the New York hospitals it was found that in about 3 per cent of all of the laparotomies there was some degree of dehiscence of the wound. Some authors were of the opinion that in most of these cases infection of the wound played a prominent rôle.

When one attempts to guess the percentage of infection in clean surgical wounds, one is prone to underestimate the damage, as is well illustrated in Meleney's article.<sup>1</sup> In trying to find the source of the contamination, many problems confront the investigator. Without a doubt, most infections arise from outside of the body, unless some hollow viscus which contains bacteria has been opened. They may be introduced from the air, from contaminated instruments, from the surgeon's hands or from the contiguous parts of the patient's body. To minimize the chances of contamination, all of these sources must be separately and individually studied. To evaluate then the results of such a study, it is necessary to have certain definite standards by which one may judge the character of a wound.

For the purposes of this study a questionnaire was sent to the heads of seventeen teaching surgical services in different parts of the country, setting forth specific questions as to their methods of preparation of

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From the Department of Surgery, Northwestern University Medical School.

1. Meleney, F. L.: Infection in Clean Operative Wounds, Surg., Gynec. & Obst. 60:269, 1935.

the operative field.<sup>2</sup> They were also invited to submit their definitions of an infected wound.

Gerster,<sup>3</sup> in the introduction to his classic volume "Aseptic and Antiseptic Surgery," wrote: "To a large number of medical men, the aseptic and antiseptic methods present an incongruous chaos of seemingly contradictory and often incomprehensible detail, arbitrary and varying, according to the predilections or whims of this or that teacher." A perusal of the answers to the questionnaires might at first impress the casual reader in a similar manner. But, just as the advent of antiseptic and aseptic surgical methods brought the mortality from amputations from 35 per cent to about 15 per cent, so has the zealous attention to detail in aseptic technic lowered the incidence of serious and of trivial infections of wounds, for instance, in the clinic of Dr. F. Meleney from 4 to 1 per cent for serious infections, and from 10 to 5.4 per cent for trivial infections.<sup>4</sup> Yet Meleney stated: "We do not feel that we have reached the irreducible minimum yet, and will strive to reduce the incidence still farther." There has been no standardization in the preparation of operative fields, and there cannot be as long as surgeons are striving to attain more perfect methods. Nevertheless, some attempt should be made to correlate the procedures and to survey the constructive efforts of teaching institutions.

DuMortier<sup>5</sup> has shown that the resistance of a healing wound to infection is minimal for the first six hours postoperatively. Billroth had already demonstrated that virulent organisms placed on granulation tissue in the dog caused no infection, while the same bacterial strain

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2. Questionnaires were sent to the following men, who represent their respective clinics: Dr. Alton Ochsner, Tulane University, New Orleans; Dr. Charles W. Mayo, Mayo Clinic, Rochester, Minn.; Dr. Elliott C. Cutler, Harvard University, Boston; Dr. Sumner Koch (general surgery), Dr. Loyal Davis (neurosurgery), and Dr. Arthur H. Curtis (gynecology), Northwestern University, Chicago (Passavant Memorial Hospital); Dr. Vilray P. Blair, Washington University, St. Louis; Dr. I. S. Ravdin, University of Pennsylvania, Philadelphia; Dr. Claude S. Beck, Western Reserve University, Cleveland; Dr. Elmer Hess, St. Vincent's Hospital, Erie, Pa.; Dr. Frank Lahey, Lahey Clinic, Boston; Dr. Vernon C. David, Rush Medical College, Chicago; Dr. J. Shelton Horsley, University of Virginia, Richmond, Va.; Dr. Dallas B. Phemister, University of Chicago, Chicago; Dr. Frederick Christopher, Northwestern University, Chicago; Dr. R. W. McNealy, Northwestern University, Chicago; Dr. Owen H. Wangenstein, University of Minnesota, Minneapolis; Dr. Hugh McKenna, Northwestern University, Chicago; Dr. John Hartzell, Detroit.

3. Gerster, A.: *The Rules of Aseptic and Antiseptic Surgery*, New York, D. Appleton & Co., 1888.

4. Meleney, F. L.: *The Control of Wound Infections*, *Ann. Surg.* **98**:151, 1933.

5. DuMortier, J. J.: *The Resistance of Healing Wounds to Infection*, *Surg., Gynec. & Obst.* **56**:962, 1933.

caused extensive infection and death in fresh wounds. It may therefore be emphasized that the technic of the operating theater and the immediate postoperative care are of vital importance in reducing the incidence of infection.

The factors at work are the dosage and virulence of the contaminating bacteria and the resistance of the tissues invaded. This might be called the bacteria-tissue balance. Did not the most powerful bactericidal agents lower the immunity of tissues by damaging them, the equation would be a simple one indeed. The problem resolves itself into a method which will reduce to a minimum the dosage and virulence of the bacteria and yet not damage the adjacent tissues. It is unfortunate that one cannot evaluate the success of the various methods by contrasting statistical results. This will be impossible until some definite criteria of an infection of a wound have been described and some specific method for tabulating results devised.

Almost all of the heads of the seventeen clinics who cooperated in detailing their technic differentiated between clean and infected wounds simply by differentiating healing by primary and that by secondary intention. The heads of two services stated that they depended on laboratory examination to determine the presence or absence of bacteria. Another stated that all wounds contain bacteria, so that he could not subscribe to such a differentiation. Definite criteria, valuable for statistical purposes, are employed in only three clinics. In two the criteria are very simple, but in one they are more complex. The criteria of one of the surgeons are: (*a*) the collection of serum or stitch abscesses, (*b*) frank infection not affecting the end-result and (*c*) complications of the wound affecting the end-result.

This surgeon added: "This rule is rigidly adhered to and reported on at the meeting of the junior members of the surgical services, and discussed at the monthly meeting of the surgical staff."

Another of the surgeons classified infected wounds into (*a*) wounds which in no way disturb the ordinary processes of healing, such as stitch infections, and (*b*) deep infections, which require opening of the wound for drainage.

One surgeon reported a complete system which, I believe, is well worthy of general adoption, if it is accurately carried out by the attending and resident staff: All wounds are classed into three groups: (*a*) clean wounds, such as those made for hernia, thyroidectomy, etc.; (*b*) partially or potentially contaminated wounds, such as those made in operations on the bowel, bladder, etc., (*c*) wounds in a grossly infected field, such as those made for abscess, empyema, etc. These are subheaded by the following code: (0) healing by primary intention; (1) secondary hemorrhage; (2) sterile hematoma; (3) hematoma which becomes infected after evacuation; (4) minor infections of the

wound, such as a stitch abscess (5) moderate infection; (6) serious, spreading infections of the wound; (7) disrupted wound; (8) necrosis of the skin, and (9) a persistent sinus or fistula. Thus a hernia which heals without any evidence of infection would be classed as A0; a hernia with a stitch abscess as A4, and a disrupted wound following a perforated gastric ulcer as B7. This surgeon considers a wound infected if it exudes as little as a drop of serum or shows the slightest amount of inflammation around a stitch. He further stated that it is the finding at his clinic that this system focuses the attention and stimulates close observation of wounds by the staff.

Some classification as this is urgently needed if uniformly good results are to be obtained. Simply to differentiate between primary and secondary union is not sufficient. Colp<sup>6</sup> expressed the opinion that infection of the wound does not play a major rôle in disruption of the wound. Grace,<sup>7</sup> however, found infection of the wound to blame in seventeen of forty-six cases of a similar nature. Yet most of the wounds which healed did so by secondary intention, irrespective of infection.

What are the precautions which are used in the general operating room in these seventeen clinics? The sterilization of linens and instruments has been omitted from consideration, for this has become fairly well standardized and is easily amenable to bacteriologic check. The scrubbing technic has also been eliminated, as this too is more or less standardized, although the relative merits of the dry and wet glove technics are still a matter of controversy.

#### GENERAL OPERATING ROOM TECHNIC

In fifteen of the seventeen clinics the heads of which responded to the questionnaire, the same room is used both for clean and for septic operations. In all these fifteen an attempt is made to perform the clean operations first. When an operating room has been contaminated, an isolation technic is the rule. In most of the institutions the furniture and floor are washed with either the compound solution of cresol U. S. P. or a 5 per cent solution of cresol, the dirty linen is soaked in compound solution of cresol, the clean linen is autoclaved and the soiled gauze is burned. The report from one clinic is in such detail that it is well worth repeating.

Linen, instruments, gloves and contaminated supplies are placed on the operating table by a nurse in gown and gloves and taken to a special work room, where linen and gauze are placed in a 10 per cent solution of cresol for one hour. Instruments and gloves are washed in cold water and boiled: instruments for fifteen minutes,

6. Colp, R.: Disruption of Abdominal Wounds, *Ann. Surg.* 99:14, 1934.

7. Grace, R. V.: Disruption of Abdominal Wounds, *Ann. Surg.* 99:28, 1934.

gloves for ten. Scalpels, pins, etc., are placed in a 40 per cent solution of cresol for one hour. The rubber pillow and operating table are washed with a 5 per cent solution of phenol. The floor is mopped with soap and water and 5 per cent phenol. The mop is treated with 5 per cent phenol and then sent to the laundry.

In twelve of the seventeen clinics all of the members of the operating team are required to wear special shoes in the operating room. In the five in which this requirement is not made nearly all of the men do so anyway. In one clinic the members of the attending staff but not of the house staff are required to wear special shoes.

In all of the clinics the visitors in the operating room, are required to wear special gowns, but in only eight are the interns required to don gowns while observing. In all the clinics visitors are required to wear caps, and in all but one they are required to wear masks. Four of the surgeons were very emphatic on this point and suggested its emphasis. In only one institution was there no requirement that the mask must cover the nose. The head of one clinic especially mentioned that each visitor to the clinic is personally and specially informed that the mask should cover the nose.

The heads of only two clinics stated that they had no difficulty in enforcing these regulations. In seven of the clinics the responsibility of enforcement is placed on the supervisor, and the cooperation of the staff is invited. The head of one clinic wrote "upon suggestion, then request of the surgeon." In one clinic notices are posted, and in two the head of the department personally enforces the rules. In one clinic there is a special officer of the day to enforce the operating room regulations.

The size and type of ligature material in the subcutaneous tissues have been accused of being a predisposing factor in many cases of infection of the wound, and therefore, the type used was asked of the different surgeons. Four of the surgeons use 00 plain catgut exclusively, while three use 0 plain catgut. Three surgeons used 000 plain catgut, while two use from 0 to 2 plain. One surgeon uses from 00 to 00000 plain catgut, and one uses either 00 plain or fine silk, while another uses only fine silk material.

#### OPERATIONS ON THE ABDOMEN, THORAX AND EXTREMITIES

Operations on different parts of the body require special technic of preparation. As the skin of the trunk and that of the extremities are somewhat similar, operations involving these parts are classed together. Only in one clinic is no preparation carried out on the evening previous to the operation. In seven clinics the operative field is cleaned with soap and water and shaved. In four clinics preoperative preparation is carried out only in cases in which clean bone is being dealt with, and in these cases a dressing moistened with 70 per cent alcohol is

applied for twelve hours preoperatively. In two clinics the area is washed with soft soap and water, shaved and cleaned with benzine, ether and alcohol, and then a sterile binder is applied. In one clinic the area is shaved and washed with soap and water, and then a sterile binder is applied.

In only one clinic is the preoperative preparation done in a special preparation room.

I have chosen to divide the solutions used on the skin and mucous membranes into two classes, the lipolytic, or cleansing, agents and the bactericidal agents. By the first are implied those compounds and solutions which remove oils and detritus from the surface of the skin, and with them mechanically remove organisms which reside therein as opportunists. Thus they mechanically reduce the dose of bacteria which the operator may introduce into the deeper tissues. Most of these are not significant in reducing the vitality of the subadjacent tissues and therefore do not affect the bacteria-tissue equation. Most potent bactericidal agents do, to some extent at least, injure normal tissue, thus influencing the equation. Bactericides are therefore considered separately.

The heads of three clinics reported that they do not employ any cleansing or lipolytic agents before the application of a bactericidal agent. In all of the clinics, however, some mechanical cleansing is used on the evening preceding a planned operation. In twelve clinics a cleansing or lipolytic solution is used. In another clinic, soft soap diluted with sterile water (1:6), copiously lavaged with sterile water, and with no other agent, is used. In three other clinics soft soap is used, but in two the surface is sponged with ether and in one with alcohol followed by ether. In four clinics benzine is used followed by ether. In one of these clinics iodine is added to the benzine in the concentration of 1 drachm (3.7 cc.) to a gallon (3,785 cc.). In three clinics alcohol is used followed with ether. In one clinic merely 70 per cent alcohol is used.

In seven of the clinics tincture of iodine is employed as a bactericidal agent. In one clinic tincture of iodine is alternated with tincture of metaphen. In all cases the concentration of the tincture of iodine is 3.5 per cent (which is sometimes referred to as "half strength iodine"). In two of the clinics the excess iodine is removed with 70 per cent alcohol, while in one clinic it is removed with Richardson's solution. In two clinics tincture of merthiolate is used exclusively. In two clinics solutions of the mercury bichloride are employed, in one in a concentration of 1:4,000 and in the other in a concentration of 1:1,000. In the latter institution this is followed by three paintings with 70 per cent alcohol and then with 3.5 per cent tincture of iodine in the umbilicus in cases of abdominal operations, or on the nails in cases of operative procedure

on the extremities. In one clinic a 5 per cent solution of trinitrophenol is used, while in another a 1:2,000 solution of mercuric oxycyanide is employed. One surgeon does not use any bactericidal agent, believing that mechanical cleansing and lipolysis are sufficient and that the bactericidal agents damage the tissues sufficiently to throw the bacteria-tissue equation into the favor of the former.

The actual preparation of the field is done by a "scrubbed" assistant or by the surgeon in fifteen of the clinics, while in two it is done by an "unscrubbed" nurse.

In sixteen of the clinics the edges of the wound are protected by skin towels. In only one are towels entirely dispensed with. In four of the institutions the towels are made of linen, in two of Bates muslin, and in two of plain cotton toweling, in one of cotton huck and in another of birdseye cotton. In three clinics laparotomy pads are used, and in another waterproof cellophane is used in operations for gastro-intestinal conditions. According to the technic in six of the clinics the towels are applied immediately after the incision in the skin is made, and in five, after the exposure of the deep fascia. In one clinic they are applied to the adjacent skin just before the incision is made, and in one, just before the peritoneal cavity is opened. One surgeon uses a sterile stockinet on the extremity, which is incised with the skin. In eight clinics the towels are fastened to the edges of the skin by Backhaus towel clamps, while in four institutions they are clipped to the edges of the skin with Michel clips. In one service they are applied to the edges of the deep fascia by clips.

In thirteen institutions the scalpel which has opened the skin is always discarded. It is usually discarded in two clinics and is not discarded in two other clinics. In only one clinic is any bactericidal agent used on the skin before the closure is made, and in this case tincture of merthiolate is used.

As a postoperative dressing, all but three surgeons use dry gauze. Two use silver foil, while one occasionally uses an alcohol dressing.

#### OPERATIONS ON THE CRANIUM

The heads of five clinics stated that no preparation is carried out on the evening preceding an operation on the cranium. In nine clinics the field is shaved and scrubbed with soft soap and water, and then sterile dressings are applied. In one clinic, after the shave and wash, benzine and ether are applied before the application of a sterile dressing. For the immediate preoperative preparation soap and water are used as a lipolytic agent in only one clinic. In four of the clinics ether is used; and in three this is followed with 70 per cent alcohol, while in one 90 per cent alcohol is employed. Benzine followed by ether is used in one clinic.

In six clinics 3.5 per cent tincture of iodine is used as a bactericide, and in four a part of the iodine is removed with alcohol. Tincture of merthiolate is used in two clinics, while the use of a 3 per cent solution of trinitrophenol, mercuric oxycyanide, and 1:4,000 mercury bichloride is reported from other clinics. In one clinic the new antiseptic solution suggested by Vaichalis and Arnold,<sup>8</sup> which has mercuric iodide as a base, is used.

In all but one service skin towels are used to protect the edges of the wound. In two, towels are used which are soaked in a solution of mercury bichloride. In five, they are sutured to the edges of the skin, while in another five clips are used. In two clinics they are clipped to the galea.

In all of the services the scalpel used for the incision is discarded. In six clinics silver foil is used as the postoperative dressing, while in six others dry gauze is used. In one clinic alcohol dressings are used.

#### OPERATIONS ON THE FACE

In nine clinics no preparation is carried out on the evening preceding operation on the face. In five clinics the area is carefully shaved, and in one the hair in the nostrils is always carefully clipped. In one clinic the face is shaved and washed with soft soap and water and then with benzine, ether and alcohol, and a sterile dressing is applied, the location of the operative field permitting.

Three surgeons advise the use of soap and water as the lipolytic and cleansing agent, which in one clinic is followed by benzine and in another by a mixture of ether and acetone. In one clinic benzine is used and in another ether followed by alcohol. In others no lipolytic agents are used. In one clinic alcohol (70 per cent) only is used as a bactericide, while in a second clinic alcohol alone is used only on children. In five clinics tincture of iodine is used, in four of them the 3.5 per cent and in one the 2 per cent tincture.

In three services the iodine is removed with alcohol, and in one, with Richardson's solution. In two institutions mercury bichloride is used, while in two the tincture of merthiolate is employed. In one a 1:200 tincture of metaphen is used and in one, mercuric oxycyanide.

Skin towels are used by eight surgeons, three of whom clip them to the edges of the skin, while in one clinic they are simply laid on and held over the edges of the skin. Three surgeons use silver foil as the postoperative dressing, while ten surgeons use dry gauze. One surgeon advocates a collodion seal, while one does not use any dressings at all.

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8. Vaichalis, J. A., and Arnold L.: Compound Solution of Mercuric Chloride for Skin Disinfection, *Surg., Gynec. & Obst.* 61:333, 1935.



## OPERATIONS ON THE ANUS

In six clinics preparations for anal and perineal surgical procedures on the evening preceding the operation consist of shaving and scrubbing the perianal skin with soap and water. The rectal canal is prepared in some way in all of the institutions. In one, irrigations with tap water are started thirty-six hours before the operation. In nine of the clinics, however, enemas of saline solution are given on the evening preceding the operation, until they return clear. Then a single enema is given on the morning of the operation. In contrast to this, in one clinic the use of only one cleansing enema is advised. One surgeon starts with a soap-suds enema, which is followed by lavages with saline solution until they return clear, and then a 2 per cent aqueous solution of mercurochrome is instilled. One report stated that on the evening preceding operation 2 ounces (30 cc.) of sweet oil is instilled into the rectum through a catheter, followed by a pint of water (473 cc.). A similar enema is given two hours preoperatively.

It seems interesting and perhaps even significant that in six clinics a routine preparation of the vagina in the female precedes rectal operations. Even if only the anus is to be the site of the operative field, one must consider that the field may become contaminated by infective leukorrheal secretions which pour from the vagina. In two cases this preparation consists in scrubbing with soft soap followed by a douche of sterile water. In one clinic the use of soap is followed by application of 50 per cent alcohol and in another by a douche with a compound solution of cresol. In two clinics the vagina is painted with a 3.5 per cent tincture of iodine under direct vision with a speculum.

Soap and water are used as a lipolytic agent on the perianal skin in seven clinics. In two clinics ether and benzine are advocated. In one clinic no further bactericidal agent is used, while in four 70 per cent alcohol is employed. In five clinics 3.5 per cent tincture of iodine is used, the iodine being removed with 70 per cent alcohol in one. Tincture of merthiolate is used in two clinics, and mercury bichloride in two others; in one alcohol is used first in cases in which general anesthesia is given, while in cases in which local anesthesia is employed soft soap is used as the lipolytic agent. Mercuric oxycyanide is used in one clinic, while in another tincture of merthiolate is used around the anus, while the rest of the field is painted with 3.5 per cent tincture of iodine.

In most of the clinics dry drapings are used, but in one institution a moist towel is placed over the genitalia. The postoperative dressing is a simple dry one in all but two clinics. In these, warm boric acid dressings are used. In ten clinics no constipating agent is used postoperatively. In one liquid petrolatum is given by mouth immediately, and an olive oil enema is given daily for one week.

## OPERATIONS ON THE SCROTUM AND PENIS

In seven clinics no preparation of the field is carried out on the evening preceding surgical intervention on the scrotum and penis. In six clinics the patient is shaved and given a bath. In only three clinics are sterile dressings applied. In six clinics soft soap and water are used as the lipolytic agent. In two clinics benzine and ether are used, and in one, a solution of benzine and iodine containing 1 drachm of iodine to a gallon of benzine.

As the bactericidal agent, only one surgeon occasionally uses a "very weak" solution of iodine. Three advocate the use of a 1:4,000 solution of mercury bichloride, following this with 70 per cent alcohol, while one uses a 1:2,000 solution of mercuric oxycyanide. In three clinics the alcohol-acetone solution of mercurochrome in a strength of 5 per cent is used. In two clinics simply 70 per cent alcohol is used, while in one, merely acetone is employed. In one clinic no bactericidal agent is used. Skin towels are applied in eleven clinics.

## OPERATIONS ON THE VAGINAL CANAL

In only three clinics is no preparation of the field done on the evening preceding operation on the vaginal canal. In most of the clinics the patient is shaved, and then some kind of douche is given. Boric acid proves to be the most popular, although sterile water and a dilution of compound solution of cresol U. S. P. (0.5 per cent) are close seconds. In one clinic a douche of a compound methol powder is used.

In twelve clinics the rectum is prepared by the use of enemas, until they return clear. In four clinics no preparation of the rectum is attempted.

The preparation of the field with lipolytic and bacteriostatic agents presents several problems. In the first place there are two types of tissue to be prepared, a sensitive mucous membrane and a resistant skin. The vaginal canal may be prepared by simply pouring the lipolytic and cleansing agents into the tract, or it may be painted carefully under full vision by the use of a speculum. If the former method is used, one must consider the possibility of washing living bacteria and debris into the vagina as the solution runs over the mons veneris and the labia. Therefore, this problem was an extremely interesting one to investigate.

In six institutions soft soap and water are used, the suds being poured into the vagina, and then the adjacent skin as well as the vaginal tract is scrubbed. Other clinics do not use any lipolytic agent. Douches are used in two clinics, consisting of either a dilution of compound solution of cresol U. S. P. (2 per cent) or a saturated solution of sodium borate. In both cases these are poured into the vagina with a standard rubber douche tip and the vagina is painted with tincture of

iodine under vision by the use of a speculum. The surrounding skin is then prepared with the tincture of iodine. In seven other clinics careful painting of the vaginal tract with tincture of iodine in a 3.5 per cent concentration is advocated, a 70 per cent alcohol being used for its removal in six clinics, and Richardson's solution in one. The surrounding skin is then prepared in a similar manner. In two of these clinics the iodine is alternated with mercurochrome in the alcohol-acetone solution, or with a 1:1,000 tincture of merthiolate. In one clinic mercury bichloride is applied blindly through swabs soaked in the solution. In another a similar technic is used but is followed with accurate painting of the vaginal tract with Churchill's iodine solution (containing 15 per cent iodine) under direct vision by use of the speculum. In one clinic mercuric oxycyanide is painted on the vaginal wall through a speculum. In another 70 per cent alcohol is poured blindly into the vagina and carried into all parts of the canal by swabs; the surrounding skin is then painted with tincture of merthiolate. In only one clinic is there no provision to keep the solutions from pouring over the mons veneris or labia.

In the postoperative care a "wet technic" is used in only three institutions. None of the reports indicate any special method of exclusion of the anus from the operative field except by draping.

#### COMMENT

From a review of the answers to the questionnaires, one can glean many significant points. Perhaps the most valuable one is the evident interest and care which most of the large teaching institutions display in their attempt to minimize the chances of contamination of the wound from sources outside of the body of the patient. This certainly should be emulated by smaller hospitals, especially those of the "open staff" type, as these are handicapped in having the responsibility for surgical complications divided among individual surgeons.

Lister was of the opinion that much of the contamination of the wound came from the air in the operating room and therefore used sprays of bactericidal solutions. Meleney stated, however, that contamination from the air was found to be a minor factor in comparison with other sources in the early days of aseptic surgery. When the other sources of bacterial contamination had been eradicated or minimized, contamination from the air again assumed a major rôle. Meleney<sup>3</sup> and Davis<sup>9</sup> have conclusively shown that serious infection of the wound may have its origin in the mouths and noses of the personnel of the operating room and of visitors. Meleney found that

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9. Davis, J. S.: The Importance of Adequate Masking During Operations, *Ann. Surg.* **100**:1008, 1934.

when, because of the obvious discomfort, he had permitted the anesthesiologists to remain unmasked, the incidence of infection of the wound definitely rose. Now he permits no exceptions to the rule of wearing a mask over the nose and the mouth. Walker<sup>10</sup> has examined masks submitted from sixty hospitals in the United States and found that "none could be considered as efficient in preventing the passage of organisms through the material." But a mask containing an impermeable membrane such as described by Blatt<sup>11</sup> is difficult to use because of the discomfort, and the 6 ply fine mesh mask will prohibit droplet infection. But the all-important factor is that masks should be worn by all persons in the operating room and worn so that both the nose and the mouth are covered. Talking and lecturing will necessarily increase the possibility of droplet infection, but in all probability the contamination from the air is enhanced most by the shuffling about of people in the operating room, opening and closing of doors, etc.

The wearing of a different pair of shoes in the operating room seems to be a factor to be considered, as emphasis seems to be placed on this point in twelve of the clinics. Unquestionably street dirt will be carried into the operating room from street shoes and new bacterial flora added to that already present in the dust of the operating room. It is perhaps even more significant that shoes and other articles of apparel which have become contaminated in doing unclean dressings must at least be covered when a person enters the operating room. The interns may come into the operating room wearing the same uniform in which they have just dressed a purulent wound or assisted at an autopsy, stand directly behind the surgeon or assistant and even touch his gown, and thus transmit bacteria into a sterile field.

The amount, type and size of the foreign material in the form of ligatures are definitely a factor in the prevention of infection. The controversy between the relative merits of silk and catgut still rages. Whipple<sup>12</sup> and many others<sup>13</sup> have been emphatic in their championship of fine silk as ligature and suture material. Yet it is notable that only two of the clinics here surveyed have adopted silk.

The preparation of the field itself resolves itself into several factors of varying importance. In planned, nonimperative operations, the removal of superficial detritus and shaving of the area are believed by the majority of the surgeons to be best carried out on the evening preceding the operation. This permits the sealing over of small abra-

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10. Walker, J. J., in discussion on Meleney.<sup>1</sup>

11. Blatt, M. L.: A New Face Mask, *Surg., Gynec. & Obst.* 57:234, 1933.

12. Whipple, A. O.: Use of Silk in the Repair of Clean Wounds, *Ann. Surg.* 98:662, 1933.

13. Halsted, W. S.: Ligature and Suture Material: Employment of Fine Silk in Preference to Catgut, *J. A. M. A.* 60:1119 (April 12) 1913.

sions which may have been produced by the preliminary scrubbing, which, it has been repeatedly emphasized, should be as gentle as it is thorough. In almost every clinic the use of some lipolytic agent, which acts as a mechanical cleanser as well, is deemed advisable in the first preparation of the field. In one clinic this is believed to be sufficient preparation. The surgeon at the head of this clinic is of the opinion that all the bactericidal agents do definite damage to the vitality of the tissues. It has been repeatedly demonstrated that there is no bactericidal agent which will completely sterilize the skin. Thus, he feels that the bacteria which remain will find excellent culture mediums in the devitalized tissues.

The variety of the bactericidal agents used by the surgeons who answered the questionnaires is rather large. Their sequence and concentration vary somewhat. This may be considered as an indication that a thoroughly satisfactory agent has not yet been found. Until there is some in vivo standardization of results, their relative merits defy scientific evaluation.

It has been practically demonstrated that the tissues surrounding a wound cannot be completely sterilized by any methods now in use. Bacteria still remain deep in the sweat glands. Without doubt, in almost every operative procedure performed under the influence of a hot source of illumination and an anesthetic the patients perspire freely. The bacteria-laden sweat is readily swept into the wounds by the hands of the surgeon or by instruments, sponges, etc. It therefore seems significant that almost in every case mention was made that the wound is isolated from the surrounding cutaneous surface by skin towels.

#### SUMMARY

The aseptic technic is not a simple routine accomplished by wearing gloves and pouring an antiseptic solution on the operative field. It is rather a complex of carefully planned and meticulously carried out procedures. Only by vigilant attention and progressive thought to detail can the incidence of wound complications be diminished to a hypothetical "irreducible minimum."

The actual evaluation of the different procedures which have been discussed is difficult or impossible until some classification of such complications has been adopted, and careful studies of wound morbidity with various technics are reported. This demands the serious attention of all surgeons to the process of wound healing.

It seems unfortunate that all attendants as well as the surgical team do not sedulously regard the possibility of seriously increasing the morbidity as well as the mortality of surgical procedures by adhering to even the more simple principles of operating routine. The most

commonly observed violation and perhaps the most dangerous is the omission of the nose mask. Until such rules are automatically followed, rigid supervision is an absolute necessity. Some persons in the operating room should in every case be given the responsibility of securing the full cooperation of the attending and the resident staff as well as of the visitors for the attainment of the most perfect technic possible.

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# LESIONS OF THE THYROGLOSSAL TRACT

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The relative infrequency and the perplexities of diagnosis combine to make lesions of the thyroglossal tract an unusually interesting group of pathologic changes. In many instances it is impossible to make an accurate and complete differential diagnosis preoperatively, owing to the close similarity of the lesion to a tumefaction arising in the midline of the neck anteriorly and to the lack of specific evidence to set any one of the lesions apart. Greater familiarity with the characteristics of lesions of the thyroglossal tract should aid in their recognition and treatment.

Adequate reason for the existence of a lesion of the thyroglossal tract is found in a study of the embryology of the thyroid gland. Meyer,<sup>1</sup> by his able summary of this subject, and Wenglowksi,<sup>2</sup> through his masterful study of the development of the thyroid, have greatly clarified a controversial problem. Briefly, it appears from the former confusion that the anlage of the thyroid arises between the open ends of the second and the third branchial arch that form the base of the tongue. In the embryo of 2.6 mm. the anlage may be seen growing downward from this so-called furcula. Whether or not the structure is tubular<sup>3</sup> or solid<sup>4</sup> is of little consequence to this study. In the embryo of 6.5 mm. studied by Wenglowksi the anlage is completely separated from the floor of the mouth and shows beginning division into right and left parts. The strand connecting the anlage with the pharyngeal floor normally segments and disappears at this stage, but if some cells fail to vanish they may give rise to the lesions here discussed. When this downward growth takes place there is a mechanical dragging in of the epithelial elements of the pharynx, i. e., squamous or ciliated cells with their associated characteristics of lymphoid tissue and mucous glands.

The development of the hyoid bone beginning in the fifth week of embryonic life is of great importance. The cells of this bone develop

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1. Meyer, H. Willy: Congenital Cysts and Fistulae of the Neck, *Ann. Surg.* **95**:1-26 (Jan.); 226-248 (Feb.) 1932.

2. Wenglowksi, quoted from Meyer.<sup>1</sup>

3. Baumgartner, C. J.: Branchial and Thyroglossal Duct Cysts and Fistula in Children, *Surg., Gynec. & Obst.* **56**:948-955 (May) 1931.

4. Norris, E. H.: The Early Morphogenesis of the Human Thyroid Gland, *Am. J. Anat.* **24**:443-465, 1918.

dorsal to the already existing thyroid strand, and the two become intimately related. Further growth of the hyoid bone and its rotation to assume its adult position cause the strand, now fused with the periosteum of the anterior surface, to be compressed and drawn posteriorly. The continuity of the thyroid strand is thus definitely broken. This fact is of significance when treatment is considered and also because a division point is formed below which about 75 per cent of the lesions occur.<sup>5</sup>

It is natural when dealing with a lesion of faulty development that other etiologic characteristics are of little differential importance. Thus, the two sexes are about equally affected, in spite of a few reports that mislead the reader to believe that males predominate.<sup>6</sup> Likewise, a lesion of the thyroglossal tract usually appears during the earlier years of life, although the developmental abnormality may remain quiescent for a long period before being stimulated to grow. For this reason lesions are reported as appearing from the first to as late as the eighth decade.<sup>7</sup>

Reference has been made to the comparative rarity of abnormalities of the thyroglossal tract. Sistrunk<sup>8</sup> recorded thirty-one cases observed in eighty-six thousand consecutive patients seen in the Mayo Clinic. Clute and Cattell<sup>7</sup> reported seventy-four cases seen among sixty-five hundred patients with goiter. The small group here recorded were observed while twenty-five hundred patients with goiter were being treated. Studies carried on at the present time indicate that the lesions could appear with much greater frequency, but the stimulus to grow is fortunately lacking in the vast majority of persons.

Because the thyroid gland begins in the base of the tongue and finally rests near the base of the neck, it is obvious that cell remnants anywhere along this course may produce lesions in later years. As noted, most of the changes appear below the hyoid bone, where commonly the tumefaction is cystic. Either spontaneously or, far more commonly, as a result of a surgical procedure, a sinus may develop from this cystic swelling. Fistulas have been reported.<sup>3</sup> Heterotopic thyroid tissue may

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5. Bailey, H.: Case of True Congenital Thyroglossal Fistula and of Subhyoid Thyroglossal Cyst, *Proc. Roy. Soc. Med.* **18**:6-7 (Oct.) 1924.

6. (a) Rankin, F. W., and Crisp, N. W.: Diagnosis and Surgical Treatment of Cysts of the Thyroglossal Duct, *West. J. Surg.* **40**:105-109 (March) 1932. (b) Klingenstein, P., and Colp, R.: Congenital Cysts and Fistulae of the Neck, *Ann. Surg.* **82**:854-864, 1925.

7. Clute, H. M., and Cattell, R. B.: Thyroglossal Cysts and Sinuses, *Ann. Surg.* **92**:57-66, 1930.

8. Sistrunk, W. E.: The Surgical Treatment of Cysts of the Thyroglossal Tract, *Ann. Surg.* **71**:121-123, 1920.



be found along the path of the embryonal strand, and reports of lingual thyroid tissue are not uncommon.<sup>9</sup>

The gross pathologic appearance of the lining wall of the cyst is smooth and shiny; thyroid tissue may be found within the wall. The contents are usually so modified by secondary infection that the original pathologic process is greatly obscured. Usually the cystic content is necrotic material, in which cholesterol crystals may be present. Histologically, the cyst is lined by squamous epithelium or infrequently by ciliated cells. Secondary infections occur so often that chronic inflammatory changes are usually present within the wall of the cyst.

A swelling in the neck is the only complaint of a patient with such a cyst unless infection is present. Secondary infection usually follows incomplete operative removal, with the formation of an intermittently or persistently draining sinus tract. In a few cases incision and drainage of a spontaneously occurring abscess will be necessary before removal can be attempted. This was true of nine cases in a series of two hundred recorded by Rankin and Crisp<sup>6a</sup> and in one of this series.

An accurate clinical differentiation of the tumefactions that appear in the midline of the neck anteriorly is difficult and frequently impossible. The clinical diagnosis is of less importance than recognition of the pathologic process at the time of operation. Surgical treatment is indicated for all patients, but the operative technic varies greatly with the lesion found. A cyst of the thyroglossal tract found low in the neck may simulate a cystic adenoma of the median lobe of the thyroid, and aberrant thyroid tissue in the same location has often been considered as an adenoma of the thyroid. The latter error could easily have been made in the following case:

Mr. K., aged 47, was admitted to the Albany Hospital on Aug. 22, 1935, because of a painless swelling in the midline of the neck. This had been present two months and had not changed noticeably in size. On examination an almond-sized firm enlargement was found to overlie the thyroid cartilage in the midline of the neck. Below this nodule was a pea-sized swelling of the same firm character at the level of the isthmus of the thyroid. A clinical diagnosis of tumor of the thyroglossal tract was made and excision revealed an adenoma, which was proved histologically to be a colloid adenoma, in some areas of which moderate hyperplasia was observed.

It is almost impossible to distinguish a dermoid or a sebaceous cyst, when found in the appropriate place, from a cyst of the thyroglossal tract. Textbooks speak of attachment to the skin by sebaceous cysts and of adherence to the deep fascia by dermoid cysts, but it may be most difficult to demonstrate these qualities in a given case. Movements of

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9. Cattell, R. B., and Hoover, W. B.: *Lingual Thyroid Gland*, S. Clin. North America 9:1355-1362, 1929. Lahey, F. H.: *Lingual Goiter*, Surg., Gynec. & Obst. 36:395-397 (March) 1923.

the cyst during deglutition may likewise be of little aid. In both the following cases a clinical diagnosis of cyst of the thyroglossal tract was made in spite of careful attention to these supposedly differentiating points.

Mr. W., aged 23, was admitted to the Albany Hospital on May 7, 1935, because of a swelling in the neck of eight years' duration. There had been no symptoms except a slow increase in size. On palpation an egg-sized systic swelling in the midline of the neck anteriorly was present just below the hyoid bone. The cystic mass was excised, and pathologic examination confirmed the operative diagnosis of dermoid cyst.

B., aged 5 years, was brought to the Albany Hospital on June 28, 1935, by her mother, who had discovered a small nodule in the midline of the neck. This had been present two months without symptoms or change in size. A deep-seated soft nodule, too small (1 cm. in diameter) to elicit fluctuation, could be seen and felt at the level of the superior border of the thyroid cartilage in the midline of the neck anteriorly. Again pathologic examination confirmed the operative diagnosis of sebaceous cyst.

The differential diagnosis, then, of a lesion of the thyroglossal tract is hazardous, and mistakes will be made in spite of great care. Clinical errors, such as have just been recorded, are unavoidable, but they can be corrected at operation without endangering the ultimate cure of the patient.

#### TREATMENT

The ability to interpret accurately the gross pathologic process will determine not only the success of the cure but the technic employed to bring about the cure. For a lesion of the thyroglossal tract Sistrunk<sup>10</sup> advised radical removal with resection of the midportion of the hyoid bone and excision of a core of tissue through the tongue. Beer<sup>11</sup> suggested nearly the same procedure in the same issue of the *Annals of Surgery* that carried the original article by Sistrunk. For a lesion which does not originate in the thyroglossal tract, such as a dermoid or a sebaceous cyst, simple excision will result in complete relief.

The radical method of Sistrunk, in spite of the good functional result, as indicated by Bailey,<sup>12</sup> may well be reserved for those cases in which a pathologic process above the hyoid bone is grossly demonstrable. From the experience in the cases here reported, a simpler procedure is less distressing to the patient, is easier of accomplishment by the surgeon and effects a cure in those cases in which the only changes observed are below the hyoid bone. The technic in such cases is total excision

10. Sistrunk, W. E.: Technique of Removal of Cysts and Sinuses of the Thyroglossal Duct, Surg., Gynec. & Obst. **46**:109-112, 1928.

11. Beer, E.: Excision of the Thyroglossal Duct Sinus, Ann. Surg. **71**:218-221, 1920.

12. Bailey, H.: Complete Eradication of the Thyroglossal Tract, Brit. M. J. **2**:138-139 (July 25) 1931.

of the cyst together with all tissue which has its origin in the thyroglossal tract and extends up to the hyoid bone, where the base of the tract or duct is cauterized. This method was followed in the cases in this series, and as yet no recurrences have appeared.

#### REVIEW OF NINE CASES

Nine cases, of which four were in males and five in females, are summarized. The age of the patients varied from 8 to 50 at the time of treatment, but the age at the onset of the lesion varied from birth to 49. Three cases appeared in the first decade of life, two in the second, one in the fourth and three in the fifth. The duration of symptoms varied from two months to thirty years, the average being nine and one-half years. Two patients had been subjected to a previous incision, excision had been attempted on one twenty-seven years before admission, and all three had experienced intermittently draining sinus tracts. The lesion in one case was associated with a branchial cleft sinus and in another case with a pilonidal sinus. Two patients discovered the swelling after an acute infection of the upper respiratory tract. The only complaints, except when infection had occurred, was swelling.

On examination these lesions were found from the suprasternal notch to the level of the hyoid bone. Two were in the suprasternal notch, five over the thyroid cartilage and two immediately below the hyoid bone. They varied in size from a narrow sinus tract to that of a lemon-sized cystic mass.

Excision of the cyst together with the sinus tract, when present, was done in each case, the method indicated previously being used. In each instance the pathologist reported a cyst or sinus of the thyroglossal tract. In six cases there was an acute or a chronic inflammatory reaction in the tissue of the wall of the cyst.

#### SUMMARY

1. Tumefaction arising in the midline of the neck anteriorly requires surgical treatment. Differential diagnosis clinically will often be impossible, but accurate recognition of the lesion at the time of operation is imperative if a cure is to follow.

2. Simple excision of all tissue of the thyroglossal tract below the hyoid bone is sufficient for cure when there is no evidence of a pathologic process above the bone.

The case reports in this paper are presented with the permission of Dr. George E. Beilby, from his private practice in the Albany Hospital.

# SIXTY-FIRST REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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This report of progress is compiled from a review of 171 papers selected from 263 titles relating to orthopedic surgery and appearing in medical literature approximately between March 1, 1936, and July 1, 1936. Only those which seemed to represent progress were chosen for review.

## CONGENITAL DEFORMITIES

*Treatment of Congenital Elevation of the Scapula.*—Seaphetti<sup>1</sup> reports 4 cases of congenital elevation of the scapula in patients aged 4½, 6, 13 and 13 years, respectively. An operation for the correction of this deformity was performed by Putti, whose technic is as follows: A curved incision is made from above the superior angle of the scapula downward convexly toward the spine to below the inferior angle of the scapula. After the fascia and the subcutaneous tissues are divided, the mesial and inferior portions of the trapezius muscle are cut from the scapula and, with the superior portion of the latissimus dorsi muscle, are retracted mesially. The rhomboid muscles are then cut from the scapular attachments. The bridge of bone extending from the superior angle of the scapula to the lamina or the transverse process of the third dorsal vertebra is resected. The scapula is drawn downward to its normal position and maintained by two silk or heavy catgut sutures, one of which is passed through the inferior angle of the scapula and sub-

1. Seaphetti, O.: Chir. d. org. di movimento 21:287, 1935.

periosteally around the fifth or sixth rib and the other from the superior angle of the scapula to the fascia of the erector spinae muscle. In closing the wound, the rhomboid muscles are resutured to the scapula. If necessary, a plastic myotomy is done on the trapezius muscle to obviate an upward pull. A plaster shoulder spica is applied. Roentgenograms and photographs accompany the article by Seaphetti. The operation is done for cosmetic and functional purposes. It is the opinion of Putti and of Seaphetti that in cases of congenital elevation of the scapula, as in those of all congenital deformities, the operation should be done as early as the lesion is recognized to prevent secondary deformities, such as scoliosis. The results, as judged from the roentgenograms and photographs, appear to be excellent.

[ED. NOTE.—The operative procedure presupposes the existence of a bony bridge from the scapula to the vertebra; this exists in a few of the cases in our experience. It is not always possible to correct the deformity with the more extensive periscapular liberating method of Schrock. It is doubtful whether this simpler and less complete procedure would suffice in all cases.]

*Radio-Ulnar Synostosis.*—Sorokin<sup>2</sup> recognizes two types of radio-ulnar synostosis. They can best be differentiated roentgenographically. In the first type the radius has no formed head, the upper end of the radius being fused wholly with the coronoid process of the ulna for from 2 to 6 cm. This type of deformity is shown best in lateral roentgenograms. In the second type the head of the radius is deformed, the radius being fused to the ulna only in the region of the tuberosity. Other exostoses are often present along the radius. Radio-ulnar synostosis is a congenital deformity frequently associated with other osseous abnormalities. Three cases are reported in detail, and a review of the literature is given.

*Tarsal Ossification in Patients with Congenital Clubfoot.*—Müller<sup>3</sup> followed the development of the feet in 57 patients with clubfoot for five years. The ossification of the tarsal bones was followed serially in 6. In 5 there was a retardation of ossification of the third cuneiform bone. In 1 there was a general delay of ossification of the distal tarsal bones. Extreme hypoplasia was not found. The first cuneiform bone was enlarged in 10 patients, the enlargement being in direct proportion to the deformity. This seemed to be a compensatory hyperplasia for the injury to the scaphoid bone. In patients treated early, with early resumption of function resulting, no abnormality in ossification was found. There was no evidence of an abnormal anlage in the develop-

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2. Sorokin, F. F.: *Acta radiol.* **17**:191, 1936.

3. Müller, E. W.: *Ztschr. f. orthop. Chir.* **64**:244, 1936.

ment of the tarsal bones. All changes in the bones were secondary to contractures or to neurologic disturbances.

*Extrophy of the Bladder in Relation to Locomotor Function.*—Kron<sup>4</sup> studied the pelves of children with extrophy of the bladder to determine what disturbances occurred in standing and walking. With the wide separation of the two rami of the pubis which occurs in this condition, there are a compensatory enlargement of the sacro-iliac joints and marked thickening of both pubic and sacro-iliac ligaments. No functional disturbances were observed, except in the rare instances of pregnancy, with its concomitant relaxation of the pelvic joints.

*Genetics of Congenital Deformities.*—Lange<sup>5</sup> in a monograph reviews the theories as to the etiology of a great number of congenital malformations. Many data of family trees and the varying geographic distribution of certain congenital deformities are presented. The author gives evidence which suggests strongly that congenital dislocation of the hip and club feet in most instances are inherited. The same is true of many other deformities. The author reasons that the tendency to such deformities is carried as a recessive trait in the physically sound members of families in which such deformities appear. He advocates marriage only with persons in whose family there is no such tendency to deformity in order to prevent this trait from becoming dominant and producing these congenital malformations.

#### METABOLIC DISTURBANCES OF BONE

*Six Years' Experience with Viosterol in the Prevention and Treatment of Rickets, Tetany and Allied Diseases.*—A study of several hundred cases of rickets by Shelling and Hooper<sup>6</sup> over a period of six years led to the following findings: 1. For full term infants a daily dose of 5 drops of viosterol was found efficacious in preventing rickets. 2. In a few prematurely born infants and babies growing at a too rapid rate a varied degree of rickets appeared when only from 5 to 10 drops of viosterol was administered daily. The authors, therefore, feel that from 15 to 20 drops of viosterol daily is needed for the first three or four months of life, after which time the dose may be reduced to that given to full term infants. 3. In 134 cases of active rickets in which healing was studied by roentgenograms, the efficacy of a dose of viosterol was found to vary according to the severity of the disease; for example, healing occurred in cases of mild involvement in from one and one-half to two months when small doses were used,

4. Kron, E.: Ztschr. f. orthop. Chir. 64:201, 1936.

5. Lange, M.: Ztschr. f. orthop. Chir. 63:1, 1935.

6. Shelling, D. H., and Hooper, K. B.: Bull. Johns Hopkins Hosp. 58:137, 1936.

whereas in cases of severe involvement from three to five months was necessary, with comparatively larger doses of viosterol. In the group of infants receiving 10 drops daily the healing time was five months; in infants receiving 15 drops, it was four and three-tenths months, and in those receiving 20 drops it was three and one-tenth months; but in the groups receiving from 30 to 60 drops the time was no shorter, indicating that larger doses than 20 drops of viosterol daily were not efficacious in producing more rapid healing. It is interesting to note that when larger doses of viosterol were given in cases of severe rickets deformities of the chest and extremities did not appear. 4. Total refractoriness was not encountered in the entire group, and partial refractoriness was seen in only 1 case. 5. No toxic manifestations were encountered, even though some infants received from 30 to 60 drops daily for several months.

#### HEMATOGENOUS CHANGES AFFECTING BONE

*Changes in the Bone in Sickle Cell Anemia.*—Changes in the bone found on roentgen examination in cases of sickle cell anemia and erythroblastic anemia are similar and are not alone diagnostic of either condition.<sup>7</sup> Sickle cell anemia is usually seen in Negro children, while erythroblastic anemia is usually encountered in children of Mediterranean peoples. The prominent changes in the bone consist of changes in the skull, such as thickening of the frontal and occipital areas, and changes in the long bones characterized by cortical thinning, expansion of the shafts and marked medullary trabeculation. Striations were also noted in the pelvis and scapulae. In cases of sickle cell anemia the changes in the bone were found predominantly in the skull.

*Changes in the Bone in Leukemia in Children.*—The bones of 43 children with leukemia were studied roentgenographically.<sup>8</sup> In 70 per cent of the patients there was a narrow zone of diminished density proximal to the metaphyses of the long bones. There was generalized osteoporosis in 2 patients and slight periosteal elevation in 2 others.

[ED. NOTE.—The aforementioned two articles should be of general interest, primarily as changes in the bone are shown to occur in a rather typical way with numerous generalized diseases.]

#### TUBERCULOSIS

*Tuberculous Cysts of the Knee Joint.*—Two cases are reported by Elliott<sup>9</sup> in adults in which roentgenographic examination showed multiple epiphysial cysts of the femur and tibia and the body of the patella.

7. Grinnan, A. G.: Am. J. Roentgenol. **34**:397, 1935.

8. Baty, J. M., and Vogt, E. C.: Am. J. Roentgenol. **34**:310, 1935.

9. Elliott, A. E.: Am. J. Roentgenol. **34**:209, 1935.

These cysts had the appearance of osteitis fibrosa cystica. No other joints were involved. There was no history of tuberculosis elsewhere in the body and likewise no evidence of articular surface damage or disease of the knee joint. In both instances, following a lesser trauma, one of the cysts ruptured into the knee joint. On biopsy, tuberculous infection was proved. In both knees, however, there was preoperative evidence of soft tissue reaction. In one case, after a period of rest, the knee functioned normally for three and one-half years; then after injury generalized tuberculosis of the joints developed.

[ED. NOTE.—This article points out, again, that tuberculous infection of bones and joints may be most atypical and simulate roentgenographically other pathologic processes.]

*Tuberculosis of the Acetabulum.*—Logroscino<sup>10</sup> reports 3 cases of tuberculous involvement of the acetabulum. Autopsy was performed in 1 of these cases. Excellent roentgenograms and a colored diagram are shown. In cases of this type the lesion starts as a relatively silent and symptomless focus. The lesion may be quite extensive before the hip joint becomes involved. In the case in which necropsy was performed the destructive lesion of the acetabulum was followed by miliary involvement of the cartilage of the acetabulum and the synovial membrane of the hip joint. The lesion may be confined to the area of the acetabulum for a relatively long time, however, before spreading to the joint. In the roentgenograms soft tissue shadows indicated involvement of the joint prior to the changes in the femur, though the lesion in the acetabulum could be seen. The roentgenograms showed areas of increased density in the roof of the acetabulum as earlier lesions followed by progressive areas of lessened density in the central area of the acetabulum. The latter areas were the site of the greatest destruction and the probable site of extension into the hip joint. In this article the literature on the subject is well discussed. While the lesions are considered from every angle, no new ideas as to therapy are suggested. Treatment consisted of plaster spicas.

*Tuberculosis of the Rib Cartilage.*—From late fetal life onward blood vessels and particularly end-arteries are found to form not only a peripheral but a central network in the rib cartilages. Emboli, as Muhlfelder<sup>11</sup> has shown, may form here. Furthermore, commencing in the third decade marrow begins to appear in the rib cartilages. It may be that in some way this plays a part in localization of the tuberculous lesion in the cartilage. The lesion extends with few symptoms, forms an abscess and discharges and burrows into the intercostal and adjacent tissues, without involving the pleura. Usually no other evidence

10. Logroscino, D.: Chir. d. org. di movimento 21:527, 1936.

11. Muhlfelder, W.: Deutsche Ztschr. f. Chir. 246:129, 1936.



of systemic tuberculosis is found. The author adds the reports of 6 cases to the 18 he has collected from the literature. Therapy is surgical. Radical excision is indicated whenever possible. If infection is mixed, preliminary drainage is indicated. Methylene blue outlines sinuses preliminary to extirpation.

*Treatment of Tuberculosis of the Bones of the Feet.*—Miltner and Fang<sup>12</sup> advocate either amputation or excision of bone in the treatment of advanced tuberculosis of the bones of the foot. The article is based on a study of 147 cases in Chinese, in 86.3 per cent of whom there were draining sinuses on admission. The diagnosis was confirmed by biopsy in 84.3 per cent. In order of frequency, the following bones were involved: os calcis, astragalus, first metatarsal bone, scaphoid and first and second cuneiform bones.

#### OSTEOMYELITIS

*Sclerosing Osteomyelitis Following Fractures.*—Swett<sup>13</sup> presents the case histories of 3 patients who had fractures which apparently healed with excessive callus but caused the patient considerable pain on use. Clinically there were local tenderness and local edema. Roentgenograms revealed sclerosis of the bone throughout the original fracture site and across the medulla. Attempts to correct the alinement by open reduction were unsuccessful in relieving pain. Finally, removal of a window of cortical bone which reestablished the medullary canal between the upper and the lower fragment led to recovery. The microscopic study of the removed piece of bone showed focal necrosis. The condition is strikingly similar to sclerosing osteomyelitis described by Garré. This is apparently the first report in the literature of the syndrome occurring in association with simple fractures.

[Ed. NOTE.—This finding is very interesting. One questions the use of the term osteomyelitis without more conclusive pathologic data.]

#### POLIOMYELITIS

*Seventh Nerve as a Pathway for the Transmission of Poliomyelitic Virus.*—Toomey<sup>14</sup> presents clinical and experimental evidence that the seventh cranial nerve is a possible pathway for the virus of poliomyelitis. Seven patients with poliomyelitis had involvement of the nervous system, which suggested a spread of the virus through the chorda tympani nerve to the nucleus salivatorius, with subsequent involvement of the surrounding neurologic structures. The author was able to produce

12. Miltner, L. J., and Fang, H. C.: J. Bone & Joint Surg. **18**:287, 1936.

13. Swett, P. P.: New England J. Med. **214**:1, 1936.

14. Toomey, J. A.: Seventh Nerve as a Possible Pathway for the Transmission of the Virus of Poliomyelitis, Am. J. Dis. Child. **51**:58 (Jan.) 1936.

experimental poliomyelitis in 5 of 7 monkeys by injection of the virus along the course of the seventh nerve.

#### CHRONIC ARTHRITIS

*Spondylitis Ankylopoietica*.—From an examination of roentgenograms, histories and clinical findings of 91 patients suffering from spondylitis ankylopoietica, Golding<sup>15</sup> concluded that the condition might be recognized in the prodromal stage before the spine was affected. Almost all the patients gave a history of pains in the muscles and joints of long duration before the spinal rigidity manifested itself, and in all pathologic changes were present in the sacro-iliac joints. Thirty-three of the patients had pathologic changes in the sacro-iliac joints without involvement of the spine. He concluded not only that the changes in the sacro-iliac joints precede the changes in the spinal cord by a number of years but that some indication of the severity of the disease can be obtained by noting the degree of activity of the process in the sacro-iliac joints.

*Roentgen Aspects of Chronic Arthritis*.—Spackman<sup>16</sup> describes the roentgenographic appearance of the normal joint and the characteristic changes which occur in rheumatoid arthritis and osteo-arthritis. The findings have been correlated from 1,000 cases. The disease processes are roughly grouped from the roentgenographic standpoint into early, intermediate and advanced stages as an aid to interpretation. The appearance of each stage has been described and illustrated with photographs and diagrammatic drawings as well as by a comparison of each stage with its corresponding pathologic picture.

*Protein Studies in Atrophic and Hypertrophic Arthritis*.—Davis'<sup>17</sup> studies show that globulin (especially the euglobulin fraction) and usually fibrinogen tend to increase and albumin tends to decrease in rheumatoid arthritis (atrophic), whereas there is little or no change in the protein fraction in osteo-arthritis (hypertrophic). This tends to show that rheumatoid arthritis is an infectious disease, while osteo-arthritis is not. The sedimentation index is a simple way of determining the globulin content.

#### NEOPLASMS

*Vertebral Angioma*.—Lamy and Weissman<sup>18</sup> discuss this disease in the light of about 20 cases that have been discovered since 1926, when the condition was first recognized. The occurrence of vertebral angioma (or hemangioma) is more common than the short time that it has been

15. Golding, F. C.: Brit. J. Surg. **23**:484, 1936.

16. Spackman, E. W.: Am. J. Roentgenol. **35**:156, 1935.

17. Davis, J. S.: J. Lab. & Clin. Med. **21**:478, 1936.

18. Lamy, L., and Weissman, L.: Rev. d'orthop. **23**:121, 1936.

recognized would lead one to believe. Schmorl found it to be present in 10 per cent of about 10,000 spines that he examined, and other autopsy statistics have agreed with his figures. Essentially a benign tumor, it has rarely been discovered clinically. Angioma without symptoms seems to occur in elderly people, while angioma with symptoms occurs in persons from 20 to 25. The dorsal portion of the spine is most often involved, and the cervical portion, rarely. More than one vertebra may be affected. The only pathogenic finding of note is the frequent occurrence of other angiomas in the skin, liver, spleen, etc. There are two types of symptoms: motor or sensory, the former being more common. Diagnosis is impossible without roentgenograms. So far as the sensory symptoms are concerned, rest, support and roentgen therapy secure excellent results. When paraplegia is present, more radical treatment is necessary, unless the disease is allowed to run on to a fatal end. Laminectomy followed by radiation is the treatment of choice, with, however, no more than 50 per cent chance of cure. Laminectomy is extremely difficult, and half the persons operated on died of hemorrhage.

*Hodgkin's Disease of Bone.*—Morrison<sup>19</sup> feels that Hodgkin's disease is a loose diagnostic term for a number of hematogenous tumor growths. The osseous system is involved in from 10 to 50 per cent of the cases. Four types of bony involvement are recognized: (1) pressure erosion, e. g., an enlarging lymph node; (2) granulomatous periostitis, by direct extension from surrounding tissues; (3) invasion of the medullary cavity, and (4) osseous hyperplasia. Often there are no clinical signs, and Hodgkin's disease in bone is found only by roentgenograms. The changes shown in the roentgenograms frequently resemble carcinomatous metastases. In rare instances Hodgkin's disease may begin primarily in the bone. Three personally observed cases are reported in detail.

#### ISCHEMIC AND SPASTIC PARALYSIS

*Ischemic Contracture.*—Steindler<sup>20</sup> reports 50 cases of fracture at the elbow complicated by Volkmann's ischemic contracture from his own clinic, in 43 of which treatment was given. Eleven of the patients were treated conservatively, i. e., by means of stretching, splints and physical therapy, while the remaining 32 were treated with combined conservative and operative measures. The operations used were myotomy of the pronator muscles (4 cases), epicondylar stripping (5 cases), transplantation of tendons (4 cases), plastic lengthening of the flexor tendons (27 cases), resection of the radius and ulna (1 case), resection of the metacarpal heads (1 case), neurolysis (2 cases) and

19. Morrison, M. C.: *Canad. M. A. J.* **34**:393, 1936.

20. Steindler, A.: *Surg., Gynec. & Obst.* **62**:358, 1936.

transplantation of the ulnar nerve (2 cases). The author emphasizes the necessity of prolonged conservative treatment in each case. He reviews the clinical and experimental data on the cause and pathologic process of ischemic contracture, emphasizing the importance of prompt reduction of the fracture and maintenance of the reduction, but he points out that ischemic contracture can and does develop in spite of complete immediate reduction. He stresses the importance of careful observation of the first signs of ischemia, which are: edema, cyanosis, pain, paresthesia, hyperesthesia, motor paralysis and trophic disturbances. With the appearance of any of these signs, the dressing should be removed and the arm placed in the position of greatest comfort, usually in partial extension, for forty-eight hours.

*Volkman's Contracture.*—Meyerding<sup>21</sup> reports 69 cases of Volkman's contracture following supracondylar fracture of the humerus. The condition in most cases was a late result, the original fracture being in some other location. In the acute stage Meyerding recommends elevation of the arm on pillows or an airplane splint. Drainage of large hematomas may be indicated. Immediate open reduction may be used in selected cases. The late results are treated primarily by conservative measures, such as were advocated by Sir Robert Jones. Operations, such as tendon lengthening manipulation, neurolysis, bone resection, etc., were performed in 33 cases.

*The Spastic Child.*—In an excellently written article, Brockway<sup>22</sup> presents the results of the study of 1,000 patients with cerebral birth hemorrhage who were treated at the Orthopaedic Hospital in Los Angeles. In 39 per cent of the cases there was a history of difficult labor. The rôle of the orthopedic surgeon in the care of such patients is stressed, but Brockway feels that there should be a medical, dental, neurosurgical and psychologic consultation in each case. If the intelligence rating is 80 or above, the prognosis for improvement under treatment is excellent. Physical therapy, braces and operative procedures, particularly tenotomy, neurectomy, and stabilization of the feet, are more commonly done. The vocational, social and economic sides of the patient's life are important.

#### OSTEOCHONDRITIS

*Osteochondritis Dissecans as Related to Trauma.*—Funston and Kinser<sup>23</sup> report 23 cases of osteochondritis dissecans. Of this series, the carpal scaphoid bone was involved in 1 case, the carpal semilunar

21. Meyerding, H. W.: Volkman's Ischemic Contracture Associated with Supracondylar Fracture of the Humerus, J. A. M. A. **106**:1139 (April 4) 1936.

22. Brockway, A.: Problem of the Spastic Child, with Clinical Summary of One Thousand Cases, J. A. M. A. **106**:1635 (May 9) 1936.

23. Funston, R. V., and Kinser, P.: South. M. J. **29**:262, 1936.

bone in 1, the acetabulum bilaterally in 1, the patellae in 3, in 1 of which the involvement was bilateral, the astragalus in 1, the head of the femur bilaterally in 1, a vertebra bilaterally in 1, the condyles of the femur in 6, the lower end of the tibia in 1 and the upper end of the tibia in 1. It is the impression of the authors that trauma is the chief etiologic factor. Operation was performed in 9 of these cases.

[ED. NOTE.—The question arises whether some of the patients may not have had definite fractures not recognized at the time of injury. There are many similarities between fractures of the articular surfaces and the so-called osteochondritis dissecans as seen ordinarily.]

*Articular Lesions Following Work with Compressed Air Tools.*—Rostock<sup>24</sup> studied 290 patients suffering from articular lesions resulting from work with compressed air tools. The elbow joint was involved in 240 cases, the hand in 44 and the shoulder in 3. In general, two types of major injury are to be observed. One is due to muscle and tendon pull and results in exostosis. The other type involves the joints and results in either osteochondritis dissecans or general changes in the joint surfaces. At the elbow, olecranon spurs at the point of the attachment of the triceps muscle are ten times as common in miners as in ordinary workers. A ringed circle of osteophytes often outlines the head of the radius. The typical exostosis is at the site of origin of the brachialis anticus muscle on the humerus. In the early stages it has the appearance of myositis ossificans. Later the outlines become distinct and free bodies form. When articular changes are pronounced, they may be found in association with a grotesque bony mass in the brachialis anticus muscle. In the hand changes occur in the lunate and navicular bones; necrosis of the lunate bone and pseudarthrosis of the navicular bone appear. At the shoulder, changes in form are found in association with marginal osteophytes. Subchondral necrosis underlies these alterations. Changes similar to those seen in compressed air workers occur in stone masons, locomotive firemen and other laborers. Localized lesions are sometimes seen in athletes.

#### MISCELLANEOUS

*"Well Leg Traction" in Correcting Orthopedic Deformities.*—White<sup>25</sup> reviews the use of "well leg traction" in the treatment of many types of lesions of the bones and joints of the legs. He believes that a form of traction applied with a device easily constructed by means of plaster of paris and an ordinary shelf or wall-bracket is superior to weight and pulley traction because of the fixed nature of the apparatus and the lessened need for adjustment. When considerable force is

24. Rostock, P.: Med. Klin. 32:341, 1936.

25. White, J. W.: South. M. J. 29:45, 1936.

required over a relatively short period, a Steinmann pin is used in the affected leg. In treating lesions such as contractures, tuberculous joints, unreduced dislocation of the hip and postoperative lesions about the hip, skin traction suffices. The use of well leg traction is mentioned in such cases as correction of lumbar scoliosis and, in a reversed manner, to obtain firm apposition after arthrodesis of the knee.

*Traumatic Arterial Thrombosis of the Forearm.*—Schär and Neff<sup>26</sup> call attention to the syndrome of traumatic peripheral arterial thrombosis. The case history and the histologic section of the affected artery in each of 2 cases are reported. In the first, after forced dorsiflexion of the wrist, pain appeared in the region of the flexor muscles at the wrist. The wrist was immobilized and improved rapidly. However, commencing two weeks after the injury there appeared a tender long mass deep over the region of the ulnar artery. At the same time pain began to radiate to the tips of the third, fourth and fifth fingers. At operation a thrombosed ulnar artery was found adherent to the ulnar nerve. An old thrombus adherent to one area of the arterial wall was found where the intima and the elastic layer had ruptured. Cure followed excision of the thrombosed segment. In the second case the ramus volaris superficialis of the radial artery was affected after a blow in the snuff box area. In each instance, after an initial period of pain, a period of freedom from pain appeared. Then there followed an episode of radiating pain in the nerve due to adherence of the thrombosed inflamed vessel, which persisted until excision.

*Therapy of Aseptic Necrosis.*—Lauber and Löber,<sup>27</sup> in cases of malacia of the semilunar bone following injuries, found that of 12 cases in which extirpation of the semilunar bone had been performed, the results were satisfactory in only 2. The rest of the patients for the most part had severe pain, which interfered with their occupation. In 6 cases in which operation was not performed the results were better on the whole than in the average case in which operation was performed. Arthritic alterations and restriction of motion at the wrist were regularly found, however. The authors stated that in malacia of the tarsal scaphoid bone and the head of the second metatarsal bone, conservative treatment gave excellent results.

#### PATHOLOGY

*Regeneration of Muscular Fibers After Injury.*—Schmincke<sup>28</sup> describes the regeneration of muscle fibers as occurring in two ways.

26. Schär, W., and Neff, G.: *Deutsche Ztschr. f. Chir.* **246**:95, 1936.

27. Lauber, H. J., and Löber, H. J. A.: *Deutsche Ztschr. f. Chir.* **246**:366, 1936.

28. Schmincke, A.: *Med. Klin.* **32**:475, 1936.

In one, true regeneration occurs. New fibers are built from old by a flowing of homogeneous sarcoplasmic processes of irregular form. Into these processes sarcolemmic nuclei grow. Secondary changes then occur: first longitudinal and then cross striations appear. In most cases fibrils develop which connect with the fibrils in the old fibers. In the second type of regeneration development is of a discontinuous, rather embryonal type. Young muscle fiber cells of spindle shape appear near each other. The plasma boundaries disappear, longitudinal and transverse striations appear in the fused sarcoplasm and a sarcolemma is formed, to complete the new fibers. Why one or the other type of regeneration will appear in a given muscle injury is not known. Some believe that the embryonal type is the more complete type of repair and occurs when more of the sarcolemma structure is retained, as in infectious myositis (destruction of the rectus muscle in typhoid, for example). In most cases in human beings the first type of attempted repair takes place. However, the connective tissue elements may grow around the sarcolemmic processes, rendering the repair abortive, and finally result in a mass or scar tissue with no true muscle function.

#### ORTHOPEDIC OPERATIONS

*Election of Site of Amputation in Diabetic Gangrene.*—Matyas<sup>29</sup> does not agree to high amputation in the presence of diabetic gangrene. He states that the site of election is low, from 3 to 4 fingerbreadths above the uppermost level of gangrenous demarcation. Operation is performed without the use of a tourniquet, and consequently bleeding serves as the major corroborative evidence of the correctness of the site of amputation. Bleeding is usually free in persons with diabetes. If it is not free, arteriosclerosis is usually present and necessitates amputation higher on the limb. According to Matyas, this conservative attitude has saved limb-length and is justified in his experience. Specific antidiabetic medication, of course, precedes amputation. Three cases are reported in detail. Indications for amputation are made early and are as follows: (1) fever, (2) general condition and (3) local findings. The muscles and fascial flap are left long without suture. The author states that muscles and fascia do poorly in persons with diabetes when sutured.

*Rupture of Long Head of Biceps Brachialis Muscle.*—In reporting 4 cases of rupture of the long head of the biceps brachialis muscle, Harris<sup>30</sup> describes the operation of Trethewan. This consists of suturing the torn tendon of the long head to the coracoid process of the scapula after passing it through the short head of the biceps muscle.

29. Matyas, M.: Arch. f. klin. Chir. 184:624, 1936.

30. Harris, H. A. H.: Brit. J. Surg. 23:572, 1936.

*End-Results of Excision of Elbow.*—Bugby<sup>31</sup> reported the results of excision of the elbow in 15 instances. They were successful in 12 cases, and in all of these good power in flexion and complete extension were obtained. For a number of months after operation there was considerable lateral instability of the joint, but this grew less. Bugby feels that excision is often preferable to arthroplasty. In his cases the operation was done for tuberculosis, traumatic ankylosis, old compound fractures and osteomyelitis as a complication of typhoid.

*Arthroplasty in Ankylosis Following Gonorrheal Arthritis.*—Essbach,<sup>32</sup> working in the clinic of E. Payr, reports the results of arthroplasty in 28 patients with gonorrheal arthritis. In 4, a preliminary operation alone was carried out, but arthroplasty was not attempted. In the remaining 24 the results were good in 18, in 4 the operation was a failure and 2 of the patients were not examined. A gonorrheal joint, if absolutely quiescent, is ideal for the operation. The presence of any local tenderness, a relative lymphocytosis, chronic ascending genital gonorrhea in the female and polyarthritis are usually contraindications for arthroplasty. The operation should not be performed on the aged or in cases in which the limb will be subjected to excessive strain.

*End-Results of Leg Lengthening.*—Stephenson and Durham<sup>33</sup> report 17 cases of leg lengthening, 15 of the tibia and fibula and 2 of the femur, in children over 12 years of age. In no case was the operation a failure. Lengthening varied from  $1\frac{3}{4}$  to  $2\frac{3}{4}$  inches (2.4 to 6.9 cm.), and in 1 case the femur was lengthened  $3\frac{1}{4}$  inches (8.2 cm.). All patients were up and wearing casts in three months. The bones were regenerated in all cases in from six to eight months. Strict operative asepsis, careful roentgenographic control of the fragments and care in the selection of the patients are stressed. The apparatus used was of the modified Abbott type.

*Synovectomy of the Knee Joint in Chronic Arthritis.*—David<sup>34</sup> reports the results following 11 synovectomies of the knee on 10 patients. Eight had good functional results without pain. The author stresses the value of this operation. It is contraindicated in the presence of active infection, tuberculosis and in uncooperative patients. Prior to operation, foci of infection and mechanical abnormalities are cared for.

[ED. NOTE.—In well selected cases this operation is one of the greatest value. It is more successful in the knee joint, however, than

31. Bugby, B. F.: Ann. Surg. **103**:625, 1936.

32. Essbach, H.: Deutsche Ztschr. f. Chir. **246**:256, 1936.

33. Stephenson, G. B., and Durham, H. A.: South. M. J. **38**:818, 1935.

34. David, S. D.: South. M. J. **38**:867, 1935.



in other joints. When operation is not feasible, a similar result can often be obtained by prolonged roentgen therapy.]

*Derotation of the Tibia.*—Stirling<sup>35</sup> describes a method of “derotating” the tibia which consists essentially of making a subperiosteal incomplete oblique fracture by a series of drill holes. He found it was of particular value in cases of malunion of tibial fractures when the vascularity of the bone was not normal.

*Arthrodesis of the Foot.*—The results of 17 bone block operations on the ankle joint are discussed by Sorrel.<sup>36</sup> Ten posterior bone block operations were done by the method of Nové-Josserand (a long turned-up graft from the os calcis) combined with subastragalar and midtarsal arthrodesis. The operation was successful in all cases, and there was considerable hypertrophy of the posterior block of bone. In 1 case there was pseudarthrosis between the block of bone and the os calcis, but this did not interfere with the functional result. The conclusion was that this type of bone block was most successful but should be combined with subastragalar and midtarsal arthrodesis. Five anterior bone block operations were done after the method of Putti and 2 by means of an oblique graft running down from the anterior astragalus into the os calcis. The first was considered the best method as it could be employed in young children without arthrodesis of the subastragalar joint. All 5 of the bone block operations by the method of Putti were successful, while only 1 of the two transfixion grafts were successful.

*Posterior Bone Block of the Ankle Joint.*—Hackenbrock,<sup>37</sup> of Cologne, reviewed the results in 15 patients on whom a posterior bone block of the ankle joint had been performed. The methods of Campbell, or Nové-Josserand, and of Camera had been used. In all these patients the operation sought to correct a foot drop, which was the result of infantile paralysis. The author found functional improvement in all of these patients, except 1, who was not yet walking after the operation. He advises that posterior bone block be combined with subastragalar arthrodesis.

*Surgical Treatment of Syringomyelia.*—Frazier and Rowe<sup>38</sup> discuss the surgical treatment of syringomyelia and report 2 cases in which surgical drainage of the cystic cavities in the spinal cord was successfully carried out. They make the point of attempting to establish permanent surgical drainage by inserting a silk thread or a gutta-percha

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35. Stirling, R. I.: Brit. M. J. **1**:58, 1936.

36. Sorrel, E.: Rev. d'orthop. **23**:193, 1936.

37. Hackenbrock, M.: Ztschr. f. orthop. Chir. **64**:222, 1936.

38. Frazier, C. H., and Rowe, S. N.: Ann. Surg. **103**:481, 1936.

drain. Roentgen therapy is stated to have been effective in certain cases reported in the literature. Frazier and Rowe feel that such treatment is indicated in dealing with gliosis and conclude that probably a combination of surgical and roentgen therapy may be a better approach than one or the other alone.

#### FRACTURES AND DISLOCATIONS

*Compression Fractures of Spine.*—An ingenious method of modifying an ordinary Simmons-Fowler bed is described by Morrison and Flamson<sup>39</sup> whereby fractures of the dorsal and lumbar portions of the spine may be satisfactorily hyperextended. Two changes are made in the bed—the head end of the spring section is fastened to the frame and the center or immobile section is loosened from the frame. By fixing the center and the lower section with steel strips, on cranking up the bed a simple angulation occurs.

[ED. NOTE.—For exact information regarding the modification of the bed, we suggest referring to this article, which contains illustrations.]

*Fractures of the Lateral Condyle of the Humerus.*—Wilson<sup>40</sup> found that fractures of the lateral condyle of the humerus in childhood occurred with a frequency of 2.5 per cent in 439 fractures and dislocations of the elbow. He states that the fracture is frequently not properly evaluated and that treatment is poorly conceived. The mechanism of injury and the pathologic process are described. When there are complete rotation and displacement of the fractured condyle, the articular surface faces upward, and nonunion will result unless the fragment is derotated and the opposing fracture surfaces are held together. The late complications from cases in which treatment is unsatisfactory are cubitus valgus and palsy of the ulnar nerve, which can be treated by supracondylar osteotomy and transplantation of the ulnar nerve.

*United Fractures of the Neck of the Femur.*—McMurray<sup>41</sup> has performed the bifurcation operation 27 times for nonunion following fractures of the neck of the femur. The results were generally good, though no figures were given. The technic of the procedure is described. Oblique osteotomy is performed at the level of the lower border of the head of the femur. Osteotomy above or below the point may result in an unstable hip. Patients are left in a plaster cast in slight abduction for from three to four months afterward.

39. Morrison, W. A., and Flamson, R. J.: *California & West. Med.* **43**:416, 1935.

40. Wilson, P. D.: *J. Bone & Joint Surg.* **18**:301, 1936.

41. McMurray, T. P.: *J. Bone & Joint Surg.* **18**:319, 1936.

*Fractures of the Patella.*—Partial or total excision of the patella is recommended by Blodgett and Fairchild<sup>42</sup> as the treatment of choice for acute fractures. If there is marked comminution, “subperiosteal excision” is done at once. If a sizable distal fragment is present, it is preserved, and the proximal fragments only are excised. The authors believe that the period of hospitalization is shortened and that the functional results are at least as good as in the older methods of open reduction and suture. The excised portion does not regenerate. They stress the necessity of outline of the torn joint capsule. Of 20 cases in which partial or total excision was carried out, the results were excellent in 7, good in 4 and unknown in 9.

*Fractures of the Neck of the Femur.*—Galland<sup>43</sup> has had excellent results in the treatment of ununited fracture of the neck of the femur following the use of the Lorenz bifurcation operation. In 6 patients, painters, stable weight-bearing hips were obtained after this procedure. Only a slight to moderate limp remained, and the patients were able to resume practically normal activity. The author describes in detail the mechanics and operation technic of the method.

*Dislocation of the Head of the Fibula in Sports.*—Strauss<sup>44</sup> reports the occurrence of sudden pain in the knee and weakness in a 7 year old girl during play. No effusion appeared in the knee joint. The head of the fibula was tender. A roentgenogram revealed anterior displacement of the head of the fibula. Reduction with the patient under anesthesia followed by immobilization in extension in a cast resulted in complete recovery. The author reviews the literature of this interesting syndrome and discusses the mechanophysiology of the dislocation. It seems most likely that the actual dislocation occurs as the result of stresses transmitted up through the fibula at the moment of impact with the ground. Not until the ligaments of the tibia and fibula are torn by lever action does dislocation occur through muscular pull. The muscles involved are mainly the extensor digitorum communis, the extensor hallucis longus and the biceps femoris muscle. The prognosis is good. No lasting peroneal palsy has been reported. Despite the fact that between 15 and 20 per cent of cadavers show communication between the tibiofibular and the tibiofemoral joint, no effusion is observed in the joint.

*Dislocation of the Base of the Fifth Metacarpal Bone.*—Roberts and Holland<sup>45</sup> describe 4 cases of isolated dislocation of the base of

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42. Blodgett, W. E., and Fairchild, R. D.: *Fractures of the Patella: Results of Total and Partial Excisions of the Patella for Acute Fracture*, J. A. M. A. **106**:2121 (June 20) 1936.

43. Galland, W. I.: *Surg., Gynec. & Obst.* **30**:410, 1935.

44. Strauss, F.: *Deutsche Ztschr. f. Chir.* **246**:212, 1936.

45. Roberts, N., and Holland, C. I.: *Brit. J. Surg.* **23**:567, 1936.

the fifth metacarpal bone. In 3 of these the base was displaced slightly inward and forward; in the fourth the base was displaced forward and outward so as to lie in the palm in front of the bases of the third and fourth metacarpal bones. Open reduction was necessary in the last case.

*Arrest of Growth After Fractures into the Epiphyses.*—In a study of fractures occurring in children 14 years of age or younger, Compere<sup>46</sup> found that in 14 per cent an epiphysis was involved. Of 19 cases in which the epiphysial line was involved in the fracture, growth disturbances of various degrees were found in 18 on careful follow-up study. Compere advises that patients with fracture involving the epiphysial line be followed through the growth period and that the prognosis be guarded.

#### RESEARCH

*Attempts to Produce Paget's Disease by Pituitary and Parathyroid Extracts.*—Believing that the pituitary gland and the parathyroid glands are important factors in the development of bone, Moehling and his co-workers<sup>47</sup> administered anterior pituitary extract and parathyroid extract to 7 adult dogs. The animals were followed by studies of blood chemistry, roentgenograms and necropsy. No changes in the bone simulating Paget's disease were noted, but there was deposition or replacement of bone marrow by calcium in the dogs receiving the pituitary and the parathyroid extracts, but none in those receiving parathyroid extract alone. Three of the dogs showed renal deposits of calcium. Various other changes in the tissues were noted, such as excessive ovulation and alterations in the thyroid gland.

*Tensile Strength of Human Tendons.*—Cronkite<sup>48</sup> states that it is generally accepted that normal tendons are never ruptured by intrinsic or extrinsic tension but are evulsed from the muscular tissue to which they are attached. Experiments were carried out to determine the tensile strength in pounds per square inch for the various undiseased tendons. The strength varied from 4,000 to 30,000 pounds per square inch. The strength of fresh tendons did not differ much in strength from the fixed tendons secured from cadavers.

*Callus Formation in the Presence of Foreign Bodies.*—Koelsch<sup>49</sup> osteotomized the fibulas of rabbits and sutured the fragments with silk, catgut or Krupp steel wire. Comparisons of these with "normal" bones

46. Compere, E. L.: Growth Arrest in Long Bones as the Result of Fractures that Include the Epiphysis, *J. A. M. A.* **105**:2141 (Dec. 28) 1935.

47. Moehling, R. C.; Murphy, J. M., and Reynolds, L.: *Am. J. Roentgenol.* **34**:465, 1935.

48. Cronkite, A. E.: *Am. J. Physiol.* **64**:173, 1936.

49. Koelsch, K. A.: *Deutsche Ztschr. f. Chir.* **246**:642, 1936.

revealed that stainless steel wire interfered least with the formation, appearance and quantity of the callus formed.

*Thermotherapy for Articular Disease.*—Pattrinieri and Logroscino<sup>50</sup> report extensive experimental studies on animals of the effects of increased temperature of the tissues as produced by diathermy and the hot air method of Bier. In animals temperatures were carefully measured with the subject under anesthesia. Similar, but necessarily less complete, studies were made on human beings. The authors conclude that Bier's hot air method of producing heat is less dangerous, is less painful at higher temperatures and produces more satisfactory hyperemia and a higher temperature in the superficial as well as in the deep tissues. This extensive study includes observations on the reaction of the pulse, blood pressure, respiration, motor functions and mind. The effect on various tissues is noted. Definite increased temperature is noted in joints when the hot air bath is applied externally.

[ED. NOTE.—This long and thorough article is incapable of brief abstraction and is recommended to those interested in the effects of the external application of heat.]

*Effect of Immobilization on Normal Joint.*—Experiments were carried out on dogs by Scogliette and Casuscion<sup>51</sup> to observe the articular changes following immobilization of the knee. The immobilization was carried out for periods varying from three to twelve months. Gross and microscopic examinations were made of the joints, and the following changes were noted: 1. A primary alteration of the synovial membrane, consisting of proliferation of the superficial layers, followed successively by endothelial desquamation with retraction of the villi and atrophy of the synovial membrane with consequent diminution of secretion of the synovial fluid, was observed. A little later sclerosis of the subserous tissue was seen. 2. A second period, a little later, was accompanied by alteration of the cartilage, that is, death of the "baso-philia," irregularity of formation of the cartilaginous sheath, diminution of its thickness and the formation of defects. The alteration of the cartilage was caused by the lack of functional stimulation and the progressive diminution of the synovial fluid. 3. In consequence of immobilization of a normal joint, the atrophy of inactivity involves all of its component parts, the synovial membrane, the cartilage and the bone.

[ED. NOTE.—This article contains excellent colored photographs and photomicrographs. The sequence of events following immobilization of a joint is of great interest and importance.]

50. Pattrinieri, M., and Logroscino, D.: *Chir. d. org. di movimento* **21**:303, 1936.

51. Scogliette, O., and Casuscion, C.: *Chir. d. org. di movimento* **21**:469, 1936.

## DIFFERENTIAL ANALYSIS OF BILE ACIDS IN HUMAN GALLBLADDER BILE

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The acids of human bile consist of a mixture of cholic, desoxycholic, anthropodeoxycholic and lithocholic acids, mainly combined with taurine and amino-acetic acid (glycine), to form the conjugated bile acids. Because there was no simple practical method to determine quantitatively the several bile acids, the reports in this field have generally concerned themselves with analysis of a portion of the bile acids. Thus the method of Schmidt and Dart estimates only the conjugated bile acids, leaving unmeasured the free bile acids, which may be present in large amounts.<sup>1</sup> The various modifications of the Pettenkofer reaction produce more color with cholic acid than with desoxycholic acid, and accordingly, if cholic acid is used as a standard, the tests yield low results for total bile acids. The reaction of Gregory and Pascoe measures cholic acid only, but in the presence of a large proportion of desoxycholic acid it will yield high false results.<sup>2</sup>

As a result of the extensive investigations into the etiology of gallstones, there has been an increasing need for an accurate quantitative method which would also differentiate the various bile acids in human bile. A number of reports have appeared on the analysis of bile acids and cholesterol in human pathologic bile.<sup>3</sup> These investigations show that if the ratio between bile acids and cholesterol falls below a certain figure, there is a tendency for the cholesterol to precipitate. This precipitation can be shown clearly by dialysis.<sup>3a</sup> However, it is evident

From the Surgical Service of Dr. Ralph Colp and the Laboratories of the Mount Sinai Hospital.

1. Andrews, E.; Hrdina, L., and Dostal, L. E.: Etiology of Gallstones: II. Analysis of Duct Bile from Diseased Livers, *Arch. Surg.* **25**:1081 (Dec.) 1932.

2. Doubilet, H.: Differential Quantitative Analysis of Bile Acids in Bile and in Duodenal Drainage, *J. Biol. Chem.* **114**:289 (May) 1936.

3. (a) Andrews, E.; Schoenheimer, R., and Hrdina, L.: Etiology of Gallstones: I. Chemical Factors and the Rôle of the Gallbladder, *Arch. Surg.* **25**:796 (Oct.) 1932. (b) Riegel, C.; Ravdin, I. S.; Morrison, P. J., and Potter, M. J.: Studies of Gallbladder Function: Composition of Gallbladder Bile in Pregnancy, *J. A. M. A.* **105**:1343 (Oct. 26) 1935.

that in these reports the analyses of bile acids are most likely incomplete because of the methods used. Moreover, since the solubility of cholesterol varies with the different types of bile acids present in human bile,<sup>4</sup> it would be of interest to know the relative amount of these different bile acids in each sample. In addition, it is possible that these various bile acids might vary in their proportions in different pathologic conditions involving the liver. A differential analysis might therefore be of some assistance both in investigating the etiology of hepatic diseases and in making a differential diagnosis.

A method for the differential bile acid analysis of human bile has been reported recently.<sup>2</sup> By combining three different methods, human bile can be analyzed for bile acids combined with taurine and with amino-acetic acid, for cholic acid, for desoxycholic acid and for free bile acids. Since anthropodeoxycholic acid and lithocholic acid, which form apparently only a small portion of the total bile acids, cannot be differentiated from desoxycholic acid so far, they are included with desoxycholic acid.

#### MATERIAL

Bile from the gallbladder of forty-five patients who were operated on for cholecystitis was analyzed for bile acids by means of this method. The bile was aspirated through the fundus of the gallbladder immediately after the peritoneal cavity was opened, and an analysis was carried out on this freshly obtained material. It was difficult to obtain bile from a normal gallbladder, since the peritoneal cavity was opened only in cases in which some viscus draining into the portal system was diseased. Since it was evident that the liver must also be involved to some degree in such cases, the bile was considered to be abnormal. However, bile was obtained from several persons in whom both the gallbladder and the liver were apparently normal. These analyses together with analyses of bile from the gallbladder of patients with carcinoma of the pancreas associated with early biliary obstruction present the nearest approach to the composition of bile from the normal gallbladder.

#### METHODS

The method for the differential quantitative bile acid analysis consists in brief of the following procedures:<sup>5</sup> In order to determine the conjugated bile acids, from 2 to 5 cc. of bile is precipitated with alcohol, and the method of Schmidt and Dart is used to determine the bile acids conjugated with taurine and with amino-acetic acid. In addition, depending on the concentration of the bile, from 1 to 20 cc. is precipitated with zinc hydroxide, and the clear bile extract is used to determine both the cholic acid (the colorimetric method of Gregory and Pascoe) and the total bile acids (the iron precipitation method). The free bile acids are calculated by the difference between the total bile acids and the conjugated bile acids.

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4. Spanner, G. O., and Bauman, L.: The Behaviour of Cholesterol and Other Bile Constituents in Solutions of Bile Salts, *J. Biol. Chem.* **98**:181 (Oct.) 1932.

5. For a detailed description of the method see *J. Biol. Chem.* **114**:289, 1936.

## RESULTS

*Analysis of Bile in Cases of Chronic Cholecystitis.*—Table 1 gives the results of the analysis of twenty-one samples of bile aspirated from the gallbladder at operation for chronic cholecystitis. In all these cases the cystic duct was found to be open. The diagnosis in each case was established by the histologic examination of the wall of the gallbladder. A few facts in each case which might be relevant to the bile acid analysis are also tabulated (e. g., whether the cystic duct is open or closed, the onset of the last attack, the duration of symptoms, the ability of the gallbladder to fill, concentrate and empty, as determined by the test of Graham and Cole, and the history or presence of jaundice).

The different bile acids are tabulated as bile acids conjugated with taurine and amino-acetic acid, total bile acids conjugated, cholic acid, desoxycholic acid and total bile acids. The percentages of cholic acid and free bile acids as compared to the percentage of total bile acids are also included. The total bile acids represent the bile acids after hydrolysis and are so calculated in order to obtain the percentage of free bile acids by subtraction from the conjugated bile acids. Thus, in case 37 the first figure, representing the bile acids conjugated with taurine, is multiplied by 1.26 to give taurocholic acid, and the second figure, representing the bile acids conjugated with amino-acetic acid, by 1.14 to give the results as glycocholic acid. The total bile acids are then calculated as follows:

Taurocholic acid	=	$1.33 \times 1.26$	=	1.67%
Glycocholic acid	=	$3.38 \times 1.14$	=	3.85%
Free bile acids.....			=	2.39%
				<hr/>
Total bile acids.....			=	7.91%

Owing to a number of factors, the percentage of total bile acids vary greatly in different cases. Undoubtedly the amount of stasis, as determined by the thickness of the wall of the gallbladder, the presence of adhesions or of a stone at the cystic duct, the presence of cholangitis or fibrosis of the liver and the history of a recent acute attack are important factors to be considered. Thus, in case 40 a stone in the first valve of Heister of the cystic duct apparently acted as a one way valve and led to an accumulation of highly concentrated bile. In cases 37, 64, 65, 78, 79, 81C and 95, in which the wall of the gallbladder was noted to be thin, the percentage of bile acids tended to average about 6 per cent. On the other hand, although the wall of the gallbladder was thin in cases 39 and 41, an early biliary cirrhosis was noted at operation, and the bile was found to be thin and of light color and to



TABLE 1.—Analysis of Bile from the Gallbladder in *C.**ic Cholecystitis*

No.	Bile Acids Conjugated with			Total Bile Acids	Obolic Acid	Desoxy- cholic Acid	Total Bile Acids*	Obolic Per- cent- age	Free Obolic Acid, Per- cent- age	Duration of Symptoms	Onset of Last Attack	Calculi in Gallbladder	Roentgen Examination of Gallbladder	Comment
	Tau- rine	Acetic Acid	Amino- Acids											
37	1.33	3.38	4.71	0.40	1.47	5.63	7.10	21	34	2 yr.	2 wk.	One choles- terol stone	.....	Slight jaundice for 2 wk.; thin gall- bladder; common duct normal
39	0.40	0.00	0.40	0.25	0.25	1.07	1.32	19	70	6 mo.	9 days	1 small stone	No visualization	Cyst of choledochus; cholangitis; thin- walled gallbladder; stasis
40	4.66	2.75	7.41	3.33	3.33	7.02	10.35	32	28	10 days	3 days	1 calcium-cov- ered choles- terol stone	.....	Stone acted as one way valve, causing high concentration of bile
41	0.36	0.00	0.36	0.22	0.22	0.35	0.57	38	36	8 mo.	Daily attacks	Few small stones	.....	Thin-walled atonic gallbladder; early biliary cirrhosis
44	1.29	1.09	2.38	0.61	0.61	1.81	2.42	25	2	9 yr.	Daily attacks	2 large choles- terol stones	Gallbladder visual- ized faintly; nega- tive shadows	Histologic section showed slight acute inflammation
47	1.74	2.60	4.34	1.82	1.82	4.48	6.30	29	31	5 yr.	12 days	No stones	No visualization	Attacks accompanied by jaundice; dis- tended gallbladder with duodenum adherent
48	1.16	0.80	1.96	2.20	2.20	4.74	6.94	32	73	15 yr.	5 days	None	.....	Duodenum and colon adherent to gall- bladder; acute attack 5 days before operation
56	1.18	0.00	1.18	1.31	1.31	4.89	6.20	21	81	2 yr.	5 days	Several choles- terol stones	.....	Ampulla bound down to common bile duct; edge of liver thick and rounded
63	....	....	....	0.83	0.83	1.87	2.70	30	..	6 yr.	9 days	Many faceted stones	No visualization; ring-shaped shadows seen	Thin-walled gallbladder
64	1.05	1.72	2.77	1.58	1.58	3.66	5.24	30	47	2 mo.	4 days	1 large choles- terol stone	Gallbladder visual- ized; empties after fat meal; negative shadow	
65	0.76	2.24	3.00	1.37	1.37	2.84	4.21	32	28	9 mo.	9 days	10 small stones	No visualization	
78	....	....	....	1.94	1.94	4.18	6.12	32	..	6 mo.	5 days	None	.....	
79	1.53	3.99	5.52	1.93	1.93	5.43	7.36	26	25	8 mo.	7 days	Small stones, some in cystic duct	Gallbladder visual- ized; negative shadows seen	Thin-walled gallbladder buried in liver; duodenum and colon adherent
80	....	....	....	0.45	0.45	0.94	1.39	32	..	10 yr.	19 days	Several large stones	No visualization	Thin-walled gallbladder surrounded by adhesions; tenderness in right upper quadrant
81B	0.71	0.56	1.27	0.73	0.73	1.39	2.12	34	40	15 yr.	14 days	Small stones	No visualization; opaque shadows seen	Wall of gallbladder thin; few adhesions; attacks accompanied by chills
81C	2.12	0.80	2.92	1.45	1.45	3.00	4.45	32	32	3 yr.	6 days	1 large choles- terol stone	Gallbladder visual- ized; negative shadows seen	Slight jaundice at operation; common duct found normal
83	1.11	2.12	3.23	1.41	1.41	2.16	3.57	39	9	4 mo.	2 days	Small stones in gallblad- der and cystic duct	.....	Wall of gallbladder thin
88	1.53	2.64	4.17	1.94	1.94	2.80	4.74	41	12	4 yr.	Constant pain	Many stones	No visualization	Distended thickened gallbladder sur- rounded by adhesions
89	1.53	1.45	3.03	0.91	0.91	2.24	3.15	30	4	8 yr.	6 mo.	Many stones	.....	
93	1.17	3.06	4.23	1.33	1.33	4.64	5.97	22	29	2 mo.	.....	15 faceted stones	Gallbladder visual- ized faintly; nega- tive shadows	Wall of gallbladder markedly thick- ened
95	1.37	3.67	5.04	1.99	1.99	4.78	6.77	29	28	6 mo.	Daily attacks	12 cholesterol stones	Gallbladder visual- ized; negative shadows seen	Wall of gallbladder thin; generalized cholesterosis; chills; white blood cells in bile obtained by duodenal drainage
Average	1.39	1.82	3.21	1.38	1.38	3.33	4.71	30	34					

\* These figures do not include the weight of the conjugated taurine and amino-acetic acid.

contain a low percentage of bile acids. These two cases, illustrating the effect of involvement of the liver on the excretion of bile acids, are given in detail.

CASE 39.—A Negro aged 49 suffered for six months from attacks of severe epigastric pain radiating to the left upper quadrant of the abdomen. Slight bilirubinemia was present (1. mg. per hundred cubic centimeters). At operation, the liver was found to be enlarged, firm and slightly fibrosed. The gallbladder was thin and distended with 80 cc. of light brownish bile and contained one small cholesterol stone. A cyst of the choledochus, 3 inches (7.6 cm.) in diameter, was found. A probe passed through the sphincter of Oddi with ease. Cholecystectomy and choledochostomy were performed. Histologic examination of a biopsy specimen of the liver obtained with punch revealed a marked polymorphonuclear and lymphocytic periportal infiltration. The fistula closed only after one month, during which time the patient suffered from severe asthenia due to loss of bile. The symptoms recurred after the formation of new bilirubin stone in the choledochus as a result of infection and stasis. The condition was finally cured by choledochoduodenal intubation. The tube was passed by rectum after it remained in the common bile duct for one year.

CASE 41.—A woman aged 39 had severe attacks of pain in the region of the gallbladder for eight months. Although jaundice was not noted, the urine became dark with each attack, and on the patient's admission to the hospital bilirubinemia was found (3.5 mg. per hundred cubic centimeters). At operation the liver was found to be somewhat cirrhotic, with rounded edges. The wall of the gallbladder was thin and distended and contained 90 cc. of muddy-looking bile and a few small calculi. The gallbladder was removed and the cystic duct was drained. A biopsy specimen of the liver obtained with a punch revealed a marked polymorphonuclear periportal infiltration. The biliary fistula persisted for five weeks. On injection of iodized poppy-seed oil 40 per cent an apparent complete biliary obstruction was present, although the stools contained some urobilin. At reoperation, neither stone nor other obstruction was found in the choledochus. Biliary drainage continued for four weeks, when the fistula gradually closed. The patient has been well since, except for one attack of pain and vomiting after a nervous spell.

In the cases of chronic cholecystitis studied (table 1) the ratio of cholic acid to total bile acids varied from 19 to 41 per cent, but most of the figures fell close to the average, which was 30 per cent. The proportion of free bile acids to the total bile acids varied to a greater extent, but the average figure was 34 per cent. The percentage of free bile acids was especially high in three of the twenty-one cases of chronic cholecystitis. In case 39, in which the free bile acids were 70 per cent of the total bile acids, early fibrosis of the liver, cholangitis and stasis of the gallbladder were present. In case 48 there was recent jaundice, which may explain the excessively high percentage of free bile acids. In case 48 operation was performed five days after an attack, which may explain the high percentage of free bile acids. In these three cases, in addition, the conjugated bile acids were calculated wholly as conjugated with taurine. Taurine aminonitrogen, as calculated from

the alcohol-soluble sulfur-containing material, is often found to be higher than the total aminonitrogen. This result is undoubtedly due to the fact that there are present nontaurine sulfur compounds, such as the ethereal sulfates. The total aminonitrogen in such cases is then calculated as derived from taurine. However, it is to be remembered that amino-acetic acid aminonitrogen may actually be present, but masked by the excessively high sulfur content. The conjugated bile acids in table 1 are on the average divided equally into taurine bile acids and amino-acetic acid bile acids. Thus the average figures are 1.39 per cent conjugated with taurine and 1.82 per cent conjugated with amino-acetic acid. But it can be seen that with a few exceptions the more concentrated the bile, i. e., the nearer it approaches normality, the greater is the proportion of bile acids conjugated with amino-acetic acid as compared to the taurine bile acids. Cases 37, 47, 79, 93 and 95 are examples. On the contrary, the more abnormal the bile, the greater the proportion of taurine bile acids. In cases of severe pathologic conditions, such as cases 39, 41 and 56, in which the percentage of conjugated bile acids is very low, no amino-acetic acid bile acids can be detected by the methods used here.

*Analysis of Bile in Cases of Acute Cholecystitis.*—The results of bile acid analysis of the contents of the gallbladder in twenty cases of acute cholecystitis are summarized in table 2. The percentage of total bile acids in cases of acute cholecystitis as compared to that in cases of chronic cholecystitis was very low, averaging 1.21 per cent, or about one quarter of the average noted in cases of chronic cholecystitis (table 1). In cases of acute cholecystitis the percentage of cholic acid as compared to that of total bile acids was also low, averaging 17 per cent, or about one half of the cholic acid ratio in cases of chronic cholecystitis. The percentage of free bile acids in cases of acute cholecystitis tended to be greater than that in cases of chronic cholecystitis. There is, however, a confusing factor in computing the free bile acids in cases of acute cholecystitis. The conjugated bile acids are determined on the material extracted from bile with a large volume of boiling alcohol. This is done to extract all the proteins, which, if present, would yield aminonitrogen on hydrolysis. In the bile removed from acutely inflamed gallbladders, some unknown nonbile acid material is present, which is soluble in hot alcohol and yields aminonitrogen on hydrolysis. This extraneous nitrogen cannot be separated and is calculated as being derived from the conjugated bile acids. It follows, therefore, that the results which are much too high are false. Cases 34, 68 and 94 are examples in which the bile acids calculated by the method of Schmidt and Dart yield figures much higher than those for the total bile acids actually present. Case 67, one of hydrops in the terminal stage of

development, is an extreme example. No bile acids could be found, but after carefully extracting the material with boiling alcohol, a calculated yield of 0.12 per cent of conjugated bile acids was found. The amount of this nitrogen-yielding material may vary, of course, thus masking the true percentage of free bile acids. But where this material is absent, the percentage of free bile acids is typically very high, as in cases 46, 72, 81, 97, 98, 101 and 123. In case 98 no conjugated bile acids are present.

In cases in which the cystic duct was closed by an impacted stone, the percentage of total bile acids was quite low. In the eight cases tabulated, the average total bile acid content was 0.65 per cent, one half the total average content. The bile acid content was higher in those cases in which the cystic duct was open, probably as a result of the entry of small amounts of hepatic bile. In case 90 the percentage of total bile acids was quite high. The results here might have been due to extremely rapid concentration with cessation of absorption of bile acids as a result of the widespread gangrene. In cases 19, 34 and 72 the inflammation was due to a reflux of pancreatic juice into the gallbladder, resulting in a chemical cholecystitis.<sup>6</sup>

*Analysis of Bile from Normal Gallbladders.*—No bile was obtainable from a perfectly normal gallbladder by aspiration. However, in two cases (table 3), in one of which the gallbladder was thought to be involved and in the other of which abscess of the liver was suspected, operation revealed an apparently normal liver and biliary tract. In case 32 the patient gave a history of frequent attacks of pain in the right upper quadrant of the abdomen unassociated with icterus. At operation, since nothing abnormal was found, bile was aspirated from the gallbladder by inserting a needle through the liver. In this case the total bile acid content was 7.66 per cent, the cholic acid content was 44 per cent of the total and the free acid content was 20 per cent of the total. In case 52 the patient gave a history of anorexia, high fever and chills; the white blood cell count was 18,000 per cubic millimeter, and there was definite tenderness over the liver. Exploration for an abscess of the liver gave negative results; the liver and biliary tract were apparently normal. Cholecystostomy was performed. The fistula gradually closed. Four weeks after operation, a roentgenogram of the chest finally revealed the first evidences of widespread miliary tuberculosis. Although the total bile acid content was low in this case, the cholic acid content was 51 per cent of the total and the free bile acid content was 20 per cent of the total. Similar ratios were obtained

6. Colp, R.; Gerber, I. E., and Doubilet, H.: Acute Cholecystitis Associated with Pancreatic Reflexes, *Ann. Surg.* 103:67 (Jan.) 1936.

TABLE 2.—Analysis of Bile from the Gallbladder in Cases of Acute Cholecystitis

Case No.	Bile Acids Conjugated with		Total Bile Acids Conjugated	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Free-Cholic Acid, Per-cent-age		Duration of Symptoms	Onset of Last Attack	Cystic Duct	Calculi in Gallbladder	Comment
	Tau-ric	Amino-Acetic					Per-cent-age	Per-cent-age					
19	0.50	1.07	1.57	0.15	2.27	2.42	31	35	10 wk.	1 day	Open	None	Chemical cholecystitis with gangrene
34	0.23	0.87	1.10	0.14	0.34	0.48	29	..	15 mo.	5 days	Open	Few small cholesterol stones	Chemical cholecystitis; gangrene; fat necrosis
35	0.24	0.70	0.94	0.11	0.93	1.14	14	18	4 yrs.	30 hr.	Open	Few small cholesterol stones	Very acute process
40	0.15	0.12	0.26	0.04	0.81	0.85	5	70	2 mo.	10 days	Open	None	Acute pancreatitis; gallbladder secondarily involved
59	....	....	....	0.006	0.112	0.11	5	..	2 wk.	5 days	Open	4 cholesterol stones	Edema; gangrene; pancreas enlarged and thickened
67	0.11	0.01	0.12	0.00	0.00	0.00	..	..	10 yr.	10 days	Closed	1 large impacted calculus	Gangrenous gallbladder; white bile
68	0.27	0.12	0.39	0.00	0.32	0.32	0	..	16 yr.	7 days	Closed	.....	Slight jaundice; fever; white cell count, 19,800; early hydrops
72	0.23	0.15	0.38	0.11	1.33	1.44	8	73	19 hr.	19 hr.	Open	Small cholesterol stone	Chemical cholecystitis; marked edema
74	0.27	0.00	0.27	0.02	0.30	0.32	7	15	8 mo.	7 days	Closed	1 large impacted stone	Thick mucoid bile
81	0.33	0.00	0.33	0.23	1.34	1.57	14	81	10 mo.	7 days	Closed	Small stones; one in cystic duct	Thick tarry bile; distended gallbladder; acute inflammation
84	0.32	0.00	0.32	0.12	0.35	0.47	24	30	15 yr.	?	Closed	1 large impacted stone	Clinically chronic; pathologic section showed chronic and acute inflammation
90	1.28	5.75	7.03	1.25	7.09	8.34	15	15	18 mo.	4 days	Open	Many small stones	Large areas of gangrene in wall of gallbladder
92	0.53	0.53	1.06	0.45	1.05	1.50	30	29	5 days	5 days	Open	100 tiny stones	Slightly thickened gallbladder with outside adhesions; high fever before operation
94	1.58	0.03	1.60	0.25	1.03	1.28	20	..	.....	5 days	Open	Many small stones	Acute process; high fever; white blood cell count 23,000
97	0.11	0.00	0.11	0.00	0.33	0.38	0	71	13 yr.	6 days	Closed	Many stones; one in cystic duct	Acute inflammation without gangrene; first stage hydrops
98	0.00	0.00	0.00	0.012	0.30	0.04	29	100	3 mo.	7 days	Open	1 small stone in gallbladder; 1 in common bile duct	Gallbladder not inflamed but cholangitis present
101	0.02	0.00	0.02	0.01	0.07	0.08	13	75	1 yr.	12 days	Open	Many stones	Subacute inflammation of gallbladder; cholecdochitis
114	0.10	0.05	0.24	0.03	0.30	0.33	9	28	5 days	5 days	Closed	Many stones	Hydrops
118	....	....	....	0.50	0.53	1.03	40	..	5 yr.	24 days	Open	1 large stone	Acute pancreatitis; pancreatic ferments in bile; gallbladder faintly visualized in roentgenogram showing 1 stone
123	0.07	0.69	0.76	0.57	1.38	1.95	30	61	1 yr.	7 days	Closed	.....	Colon and duodenum adherent to gallbladder; 2 shaking chills; fever and jaundice; beginning hydrops
Average				0.20	1.01	1.21	17	50					

in the analyses of bile obtained through fistulas in the common duct after recovery from the operative procedure. These analyses will be reported in a later communication.

Analyses of bile from the gallbladder in cases of early obstruction due to carcinoma of the pancreas (table 3, cases 38, 116, 86 and 122)

TABLE 3.—*Analysis of Bile from Normal Gallbladders*

Case No.	Bile Acids Conjugated with		Total Bile Acids Conjugated	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Cholic Acid, Per-cent age	Free Bile Acid, Per-cent age	Comment
	Tau-rine	Amino-Acetic Acid							
32	2.65	3.51	6.16	3.33	4.33	7.66	44	20	Attacks of pain in right upper quadrant for 4 yr.; no icterus; biopsy of liver showed normal histologic structure
52	0.99	0.85	1.84	1.20	1.13	2.33	51	20	Anorexia; fever; chills; white cell count, 18,000; tenderness over liver; final diagnosis, miliary tuberculosis
38	3.80	5.06	8.86	4.25	5.50	9.75	44	19	Cancer of pancreas with obstruction; icterus for 3 wk.; bilirubinemia, 1.5 mg. per 100 cc.; 150 cc. of bile in gallbladder
116	2.33	4.49	6.82	6.13	6.89	13.02	46	47	Cancer of pancreas with obstruction; icterus for 7 wk.; bilirubinemia, 18 mg. per 100 cc.; 200 cc. bile in gallbladder
86	1.96	3.63	5.60	3.02	2.53	6.15	59	9	Cancer of pancreas with obstruction; icterus for 2 wk.; bilirubinemia, 7.5 mg. per 100 cc.; 100 cc. of bile in gallbladder
122	0.81	1.85	2.66	1.70	1.40	3.10	55	14	Cancer of pancreas with obstruction; icterus for 2 wk.; bilirubinemia, 10 mg. per 100 cc.; galactose and sodium benzoate tests show impairment of liver function
122A	0.71	0.00	0.71	0.87	1.16	2.03	43	65	Cancer of choledochus; icterus for 10 days; icteric index, 120; incomplete biliary obstruction
55	0.08	0.02	0.10	0.04	0.10	0.14	25	28	Cancer of pancreas with obstruction; icterus for 6 mo.; bilirubinemia, 18 mg. per 100 cc.; first stage white bile; 140 cc. of bile in gallbladder
113	....	....	....	0.008	0.027	0.035	23	..	Cancer of bile ducts with obstruction; icterus for 7 wk.; bilirubinemia, 18 mg. per 100 cc.; bile; with

revealed the proportions of cholic acid and of free bile acids to be somewhat similar to those in cases 32 and 52. However, in cases in which there had been long-standing obstruction, as in case 55 (table 3), the cholic acid content was 25 per cent of the total bile acid content. In case 113, in which obstruction was associated with acute cholangitis,

the bile acids were found to be in very low concentration, 0.035 per cent, while the cholic acid content was 23 per cent of the total bile acid content.

It is of some interest to note the huge amount of bile salts that may accumulate in the gallbladder during the height of stasis in cases of carcinoma of the pancreas. In case 116, after inclusion of the weight of the conjugated taurine and amino-acetic acid, the percentage of total bile acids was found to be 14.94. Since 200 cc. of bile was present, the gallbladder contained nearly 30 Gm. of bile acids.

In case 52 analysis of bile from a fistula in the gallbladder was of interest, since the gallbladder was undoubtedly irritated and inflamed by the presence of the drainage tube. The results are summarized in table 4. It can be easily seen that the greater the concentration of bile

TABLE 4.—*Analysis of Bile Drained During Cholecystostomy*

Case No.	Day After Operation	Bile Acids Conjugated with		Total Bile Acids Conjugated	Cholic Acid	Desoxy-cholic Acid	Total Bile Acids	Cholic Acid, Percentage	Free Bile Acid, Percentage
		Taurine	Amino-Acetic Acid						
52	Operation.....	1.00	0.85	1.85	1.20	1.13	2.23	51	20
	2d day.....	0.37	0.16	0.53	0.19	0.08	1.17	17	53
	5th day.....	0.35	0.06	0.41	0.21	0.41	0.62	34	34
	8th day.....	0.27	0.08	0.35	0.19	0.40	0.59	32	41
	15th day.....	0.22	0.33	0.55	0.20	0.52	0.72	28	24
	19th day.....	0.26	0.20	0.46	0.14	0.72	0.86	16	46
111	5th day								
	Fistula in gallbladder	0.36	0.02	0.38	0.01	0.01	0.02	50	..
	Choledochal fistula..	0.15	0.15	0.30	0.16	0.14	0.30	54	0

acids, the lower is the percentage of cholic acid as compared to the total. The bile from the gallbladder at operation apparently contained bile acids in their normal proportions, but on the second day after operation the cholic acid content fell to 17 per cent of the total bile acid content and the free bile acid content rose to 55 per cent of the total. On the fifth and eighth days, the first reaction to the operation began to subside, and the percentage of cholic acid rose to 34. On the nineteenth day, the concentrative ability of the gallbladder increased, but the percentage of cholic acid fell to 16, while the percentage of free bile acids rose to 46.

In case 111 the gallbladder and common bile duct were drained by separate tubes. The remarkable ability of the inflamed gallbladder to absorb bile acids was clearly demonstrated. Although the bile from the cholecystostomy tube was much more concentrated and darker than the bile drained from the common duct during the same period, the concentration of bile acid had diminished 93 per cent in passing through the inflamed gallbladder. In addition, it can be noted that, as in other

cases of acute cholecystitis, an abnormal material was present in the bile drained from the gallbladder, which yielded a high false figure for the conjugated bile acids.

#### COMMENT

In analyzing the figures presented here, two important facts are apparent. The first is that no reliance can be placed on any one method of analysis. The second is that in cases of chronic cholecystitis the ratio of the cholic acid and of the free bile acid content to the total bile acid content varies markedly and consistently as compared to that found in cases of acute cholecystitis.

It is apparent that analysis of bile acids by the method of Schmidt and Dart would yield definitely false results in most instances. Even in bile from the apparently normal gallbladder there seems to be about 20 per cent free bile acids, while in cases of acute cholecystitis as high as 100 per cent of the bile acids may be found to be free. In addition, the opposite extreme may also be present, in that the method of Schmidt and Dart will often yield inordinately high false results in pathologic bile. It would seem, therefore, that analyses based on this method are untrustworthy.

The various modifications of the method of Gregory and Pascoe are specific for cholic acid only. Therefore, in human bile especially, in which desoxycholic acid is present in large proportions, this method yields manifestly false results, probably less than half the total bile acids being analyzed. There is a compensatory effect, however, since the presence of a large proportion of desoxycholic acid produces a fine precipitate during the reaction and results in a higher reading for cholic acid than is actually present.<sup>2</sup> There can be no doubt, therefore, that all analyses of human bile based on the method of Gregory and Pascoe are unreliable.

The procedure of Aldrich and Bledsoe, based on the Pettenkofer reaction, probably yields better results in that desoxycholic acid present in human bile takes a slight part in the reaction. Unfortunately, it has been shown that desoxycholic acid produces only about one half to two thirds of the amount of color yielded by cholic acid. It might be argued that by this method as well as by the method of Gregory and Pascoe, the analyses would be relatively correct in comparing different pathologic conditions. It is evident, however, that since the ratio of cholic acid to desoxycholic acid varies tremendously, analyses based on these methods would be incorrect, even relatively.

It is obvious that the significant feature in the analyses presented herein is the marked variations in the proportions of the individual bile acids in each sample. It is, of course, impossible to make any conclusive comparisons between analyses of bile from normal gallblad-



ders and from gallbladders in cases of chronic cholecystitis owing to the lack of normal controls. It would seem, however, that the ratio of cholic acid to total bile acids is much lower in cases of chronic cholecystitis than in cases in which the gallbladder was found to be normal (table 3). Thus the average percentage of cholic acid is 50 in cases 32, 52, 38, 116, 86, 122 and 122A.

In comparing the analyses of bile from the gallbladder in cases of chronic and of acute cholecystitis, the differences are very definite. Aside from the marked reduction in the percentage of total bile acids in cases of acute cholecystitis noted by other investigators,<sup>7</sup> which is due to absorption by the inflamed wall of the gallbladder, it can be seen that various bile acids disappear at different rates. Since the different bile acids vary greatly in their physical properties, such a result should not be unexpected. From the analyses it appears that the bile acids conjugated with amino-acetic acid are more readily absorbed than the taurine-conjugated bile salts. Cholic acid is more readily absorbed than desoxycholic acid, and the conjugated bile acids disappear more quickly than the free bile acids, leaving the latter in preponderance. Stasis of long duration unaccompanied by infection, as in cases 122 and 55 in table 3, apparently leads to this relative resorption of bile acids. It would appear, therefore, that a differential bile acid analysis of bile from the gallbladder should yield results which would be an index not only of the degree of stasis but more especially of the amount of resorption of bile acids due to inflammation of the wall of the gallbladder.

One other point might be noted. In cases 39 and 41, in which analysis revealed rather extreme changes in the ratio of the different bile acids, tending to approach those in cases of acute cholecystitis, the wall of the gallbladder was relatively uninvolved. In each case, however, the liver seemed to be the seat of early biliary cirrhosis and showed on histologic examination a marked polymorphonuclear periportal infiltration. It is difficult to determine whether these changes in the composition of bile acid were due to stasis resulting from the gallbladder alone or whether the pathologic changes in the liver were the cause. Andrews, Hrdina and Dostal reported four cases in which abnormal types of bile acids were excreted by the liver.<sup>1</sup> In each of these cases the liver was apparently the seat of an early biliary cirrhosis. It appears likely, therefore, that the changes noted in the bile acids in cases 39 and 41 are the result of dysfunction of the liver.

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7. Rosenthal, F., and Licht, H.: Die Resorption der Gallensäuren in der normalen und entzündeten Gallenblase, *Klin. Wchnschr.* 7:1952, 1928. Andrews, Schoenheimer and Hrdina.<sup>3a</sup>

## CONCLUSIONS

In a number of cases in which the gallbladder was found to be normal, analysis of the bile from the gallbladder revealed the bile acids to consist of about 50 per cent cholic acid and 50 per cent noncholic bile acids, mostly desoxycholic acid. The bile acids were conjugated to the extent of about 80 per cent, half with taurine and half with amino-acetic acid.

In cases of chronic cholecystitis cholic acid formed about one third of the total bile acid content in the bile from the gallbladder. In cases of acute cholecystitis only about one sixth of the total bile acid content was cholic acid.

Free bile acids formed about one third of the total bile acid content in cases of chronic cholecystitis and one half in cases of acute cholecystitis.

Bile acids are absorbed rapidly by the inflamed wall of the gallbladder. This increased permeability is selective, the cholic acid being absorbed more readily than the desoxycholic acid, the bile acids conjugated with amino-acetic acid more quickly than those conjugated with taurine and the conjugated bile acids more readily than the free bile acids.

The fall in the relative percentage of cholic acid and the rise in the relative percentage of free bile acids apparently indicate that absorption of bile acids has taken place.

In two cases in which a pathologic condition of the liver was present, analysis of the bile from the gallbladder revealed the proportions of the various bile acids to be similar to those found in the bile in cases of acute cholecystitis.

# OSSIFICATION

## THE INFLUENCE OF THE MINERAL CONSTITUENTS OF BONE

J. DEWEY BISGARD, M.D.

OMAHA

To explain the process by which bone is formed two theories have long existed, the chemical, or humoral, theory and the cellular, or vital, theory. These theories diverge principally in respect to whether or not osteoblasts take a part, secretory or otherwise, in the synthesis of the mineral elements into bone. Exponents of both views agree, obviously, that ossification can take place only in the presence of an adequate supply of calcium and of the other constituents of bone, but whether the process can be initiated, hastened or otherwise favorably influenced by a local supply in excess of normal and whether synthetic bone salts introduced into the site of ossification can be utilized by the organism are controversial subjects with which this report of investigation is concerned.

From a study of much clinical and experimental material, Leriche and Policard,<sup>1</sup> early advocates of the chemical theory, were led to sider: . . . "a local calcific surcharge as the determinant of osteogenesis in a suitable fibrous medium." They expressed the belief that the supply of calcium used in the repair of a bone is liberated locally from the bone, which is undergoing repair. This theory led to the assumption on the part of many investigators that reparative ossification failed in certain instances owing to an actual deficiency in available calcium at the site of repair.

Murray,<sup>2</sup> who has stimulated a renewed interest in this subject, has presented much evidence, though inconclusive, that the repair of bone defects in animals and the repair of fractures in man are favorably influenced by saturating the site with the synthetic salts of bone, calcium carbonate,  $\text{CaCO}_3$ , and calcium phosphate,  $\text{Ca}_3(\text{PO}_4)_2$ . The favorable results obtained in his clinical cases are subject to the usual criticism of the inability to control all elements entering into the investi-

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1. Leriche, R., and Policard, A.: *The Normal and Pathological Physiology of Bone*, translated by S. Moore and J. A. Key, St. Louis, C. V. Mosby Company, 1928.

2. Murray, C. R.: *Delayed and Non-Union in Fractures in the Adult*, Ann. Surg. **93**:961, 1931; scientific exhibits presented at the Seventy-Ninth and Eightieth Annual Sessions of the American Medical Association, 1928 and 1929.

gation, such as the influence exerted by the operative exposure necessary for the introduction of the salts. Using the same salts in a series of experiments on animals similar to those carried out by Murray, Stewart<sup>3</sup> obtained no positive evidence that these salts had a favorable influence on the repair of bone. He concluded that "lime salts and boiled bone, when placed into a bone defect with either traumatized muscle or fascia, do not serve as a source of available calcium resulting in super-saturation of connective tissue and regeneration of missing bone."

Key<sup>4</sup> carried out a similar group of experiments in which large total gaps in the radii of dogs from block resections were filled with calcium carbonate and calcium phosphate in one series and in another with bone powder (bone from which the organic material had been extracted with sodium hydroxide). From the results he concluded that "neither calcium phosphate and carbonate in the proportions in which they occur in bone, nor bone powder, made by the removal of the organic material from bone, appear to stimulate osteogenesis of bone when implanted in a bone defect." Eden<sup>5</sup> found that calcium alone injected at the site of a fracture in both man and animals had no stimulating effect on repair, but that phosphates introduced into a callus hastened ossification.

In respect to ectopic ossification or the formation of bone in tissues which normally do not contain bone, the dependence of ossification on the concentration of calcium in the tissues is more apparent. Such bone has been found in most tissues and in nearly every organ of the body, but in most instances ossification has taken place in degenerated or necrotic tissue which often has previously undergone more or less calcification. There are, no doubt, other contributing factors, such as the presence of cells possessing osteogenic function, and that such a function is possessed by cells other than osteoblasts, notably the epithelium lining the urinary tract, seems fairly well established by the results of such investigations as those carried out by Neuhof<sup>6</sup> and later by Huggins.<sup>7</sup> However, the importance of calcium in initiating

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3. Stewart, W. J.: Experimental Bone Regeneration (Using Lime Salts and Autogenous Grafts as Sources of Available Calcium), *Surg., Gynec. & Obst.* **59**:867, 1934.

4. Key, J. A.: Effect of a Local Calcium Depot on Osteogenesis and Healing of Fractures, *J. Bone & Joint Surg.* **16**:176, 1934.

5. Eden, R.: Experiments on the Process of Ossification and Methods for Influencing It, *Arch. f. klin. Chir.* **126**:418, 1923.

6. Neuhof, H.: Fascia Transplantation into Viscera Defects, *Surg., Gynec. & Obst.* **204**:383, 1917.

7. Huggins, C. B.: The Formation of Bone Under the Influence of Epithelium of the Urinary Tract, *Arch. Surg.* **22**:377 (March) 1931.

ossification has been demonstrated repeatedly. Annovazzi,<sup>8</sup> Nagelotte,<sup>9</sup> Poletini,<sup>10</sup> Andrei<sup>11</sup> and others have injected calcium into various tissues of animals and some weeks later have recovered from the ears of rabbits and from the tendons of dogs small pieces of bone which have developed at the site of injection. Other substances injected into these same tissues failed to produce bone.

#### EXPERIMENTAL PROCEDURE

To investigate this problem under circumstances which permitted more accurate control of the elements involved, the following method of procedure was used. Autogenous transplants of certain tissues, as subsequently enumerated in detail, were made to the anterior chamber of each eye of one hundred and fourteen rabbits and three dogs. Immediately after removal from the donor tissue, the transplants were placed into large needles containing tightly fitted stilets. The needles were forced through the cornea at the limbus into the anterior chamber, and the graft was forced out of the needle into the chamber with the stilets. In most instances the grafts promptly became attached to the iris, from which they became vascularized (figs. 1 and 2). After this had taken place and the inflammatory reaction incident to the trauma of operation had subsided, usually within ten days, aqueous suspensions of either bone salts or bone ash were injected through very fine needles into the anterior chambers of approximately half of the eyes. The salts were those which have been found by analyses to be contained in bone and in the proportions found in bone; namely, calcium phosphate, 85 per cent; calcium carbonate, 14 per cent, and magnesium phosphate, 1 per cent.<sup>12</sup> In many instances the injections were repeated so as to keep the transplants, which usually became attached to the iris at the bottom of the eye, bathed constantly for several weeks in salts or ash (fig. 3). The transplants in the eyes into which salts were not injected served as controls. Utilization of the anterior chamber of the eye for a culture medium has been used by several investigators, among them Polacco,<sup>13</sup> Podleschka and Dworzak<sup>14</sup> and Allan and Priest.<sup>15</sup> It offers certain advantages

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8. Annovazzi, G.: Experimental Production of Bone by Injection of Calcium Salts, *Arch. ital. di chir.* **23**:537, 1929.

9. Nagelotte, J.: Ostéogénèse dans les greffes de cartilage mort, *Compt. rend. Acad. d. sc.* **169**:737, 1919.

10. Poletini, B.: Ulteriore contributo allo studio de neoformazioni ossee e cartilaginee determinate da innesti de tessuti fissati, *Arch. ital. di chir.* **7**:169, 1923.

11. Andrei, O.: Sulla produzione di osso e di cartilagine in seguito ad innesti de tessuti fissati e viventi, *Arch. ital. di chir.* **11**:483, 1925.

12. Wells, H. G.: *Chemical Pathology*, ed. 4, Philadelphia, W. B. Saunders Company, 1920.

13. Polacco, E.: Comparative Research Work on Bony Neoformations During Autoplastic Grafting of Periosteum and of Young Bone, *Arch. per le sc. med.* **53**:476, 1929.

14. Podleschka, K., and Dworzak, H.: Transplantation of Organs into the Anterior Chamber of the Eye of the Rabbit as a Biologic Method, *Med. Klin.* **30**:438, 1924.

15. Allan, E., and Priest, F. O.: Physiological Response of Ectopic Ovarian and Endometrial Tissue, *Surg., Gynec. & Obst.* **55**:553, 1932.

in that it is possible to culture tissue *in vivo* and yet have the culture suspended in a medium which can be altered and controlled to a certain degree. It also provides opportunity to observe the graft as often as one wishes.

After varying periods of time the animals were killed, and the grafts were recovered and studied microscopically.

EXPERIMENT 1.—*Transplants of bone (only) versus bone and bone salts.*

Small fragments of bone were removed subperiosteally from the tibia of each of twenty rabbits and placed into the anterior chambers of the eyes of each animal. From ten to fifteen days later bone salts were injected into fifteen of the eyes. In only nine rabbits did both eyes remain uninfected and normal. Each of these provided a pair of transplants for comparison, one of the pair cultured in a medium saturated with bone salts and the other, as illustrated in figures 1 and 4, in normal aqueous. The first pair of transplants were studied micro-

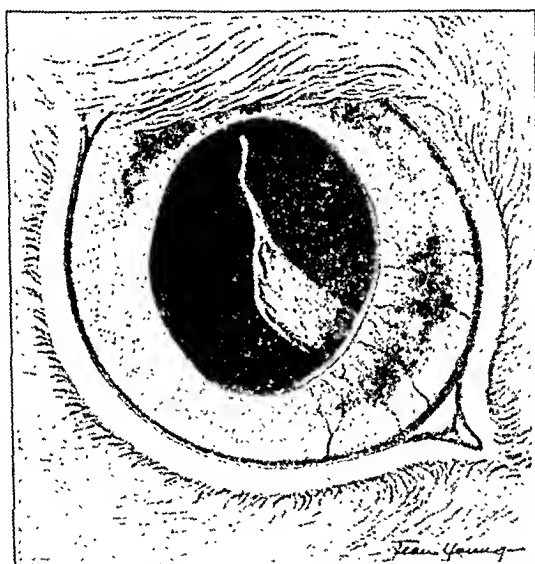


Fig. 1.—Drawing of the right eye of rabbit 14, showing a transplanted segment of bone attached directly to the iris below and by a long pedicle above. Note the blood vessels in the region of attachment of the graft.

scopically eight days and the last pair one hundred and seventy-six days after transplantation and the others at intervals intervening. There were in addition to these, twelve unpaired and uninfected eyes, two containing bone salts. Some of the latter were studied as early as four days after transplantation.

The results may be summarized as follows: The major portion of each transplanted segment of bone became necrotic, but in each specimen there were areas in which the bone cells were alive, particularly the cells near the surfaces. New bone was apparent as early as eight days after transplantation. It appeared first on the surfaces and appeared no earlier and in no greater abundance in the transplants bathed in bone salts.

The necrotic old bone gradually became absorbed and to some extent became replaced by new bone. Absorption first took place on the surface attached to the

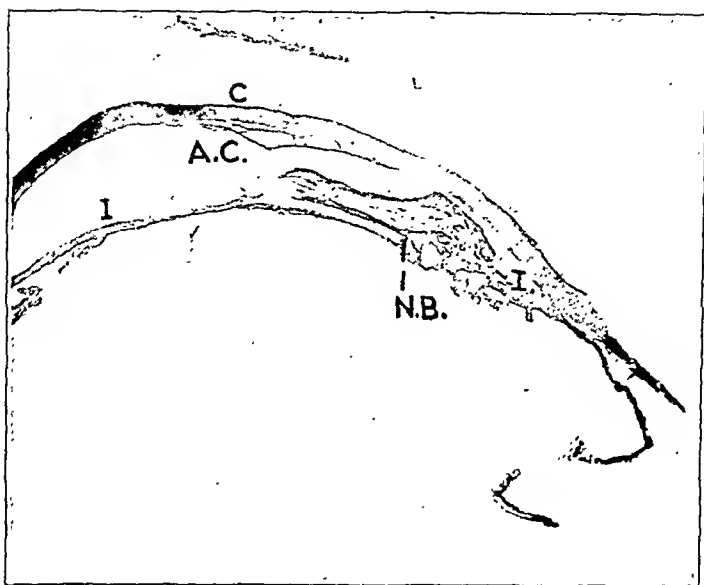


Fig. 2.—Low power photomicrograph of an eye of a rabbit showing an autogenous transplant of periosteum which is attached to the iris, *I*, from which it received its blood supply. It is suspended in the anterior chamber (*A.C.*) and has given rise to much new bone (*N.B.*). The cornea is labeled *C*. This transplant was one hundred and thirty-two days old.

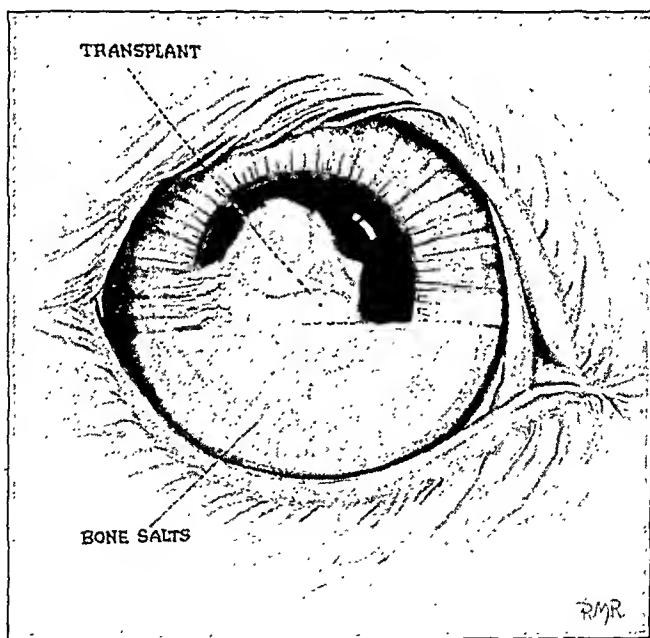


Fig. 3.—Drawing of the right eye of rabbit 32. A segment of periosteum was transplanted into the anterior chamber, and ten days later bone salts were injected in sufficient quantity to saturate the medium about the transplant. Note that the salts almost completely submerge it.

iris and seemed to extend from this area. In the tissue invading the graft there were many pigmented (melanin) cells. Bone salts were found encysted in the iris and in the fibrous tissue attaching it to the graft.

There was no evidence that the bone salts influenced either the fate of the transplant or the formation of new bone.

EXPERIMENT 2.—*Transplants of bone and periosteum versus periosteum (alone).*

Seven rabbits received transplants from their tibias of bone and periosteum in one eye and of periosteum alone in the other eye. Two eyes became grossly infected, leaving twelve transplants but only five pairs. These were sectioned at

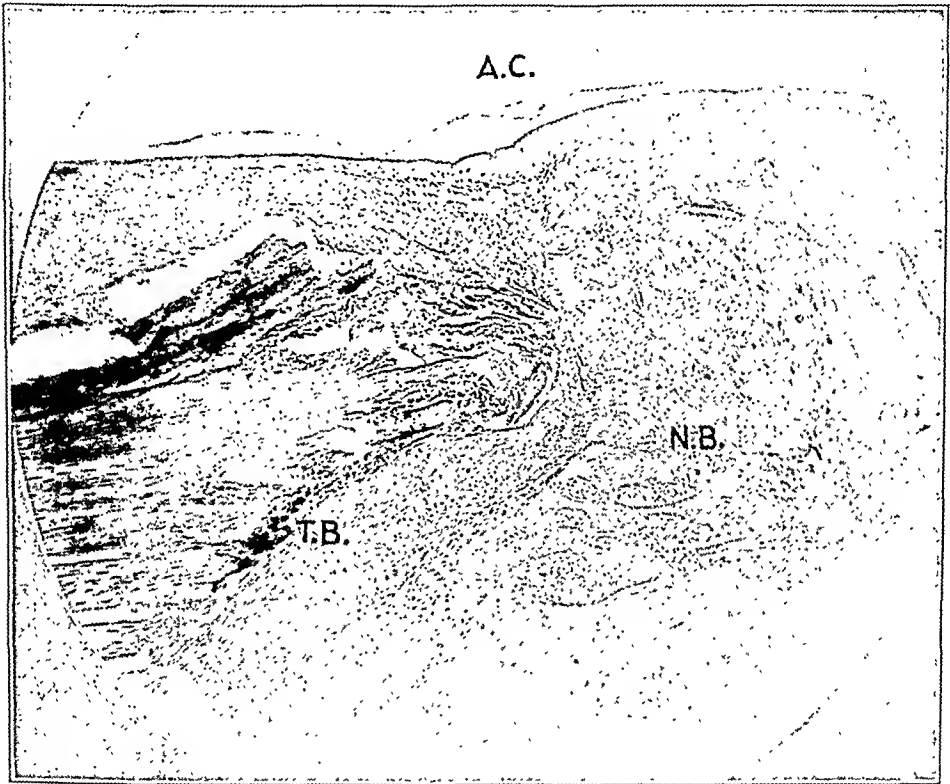


Fig. 4.—A photomicrograph of an autogenous transplanted segment of bone (T.B.) in the anterior chamber of an eye of a rabbit. It is surrounded by the fibrous tissue by which it is attached to the iris and cornea. The old bone is partially necrotic and in many areas is undergoing absorption and invasion by granulation tissue. A short distance from the transplant there is a mass of new bone (N.B.) consisting of anastomosing trabeculae with fibrous marrow. It is surrounded by a very vascular and cellular zone composed of actively proliferating osteoblastic cells. A.C. designates the anterior chamber. The transplant was twenty-one days old.

intervals varying from five to one hundred and twelve days after transplantation. A transplant which supposedly consisted of periosteum alone contained a minute sliver of old bone.

There was new bone arising from the surface of all periosteal transplants with the exception of the one observed at five days. New bone was present in all



specimens containing both bone and periosteum and obviously was much greater in amount and was arising from a much more extensive surface area than was that developing from grafts of periosteum alone. Melanin cells were present in the fibrous tissue invading the graft. Each periosteal transplant contained areas of necrotic tissue. A transplant of periosteum only with an unusually luxuriant growth of new bone is illustrated in figures 2 and 5.

The transplanted segments of bone presented the same histologic picture and succession of changes enumerated in experiment 1.

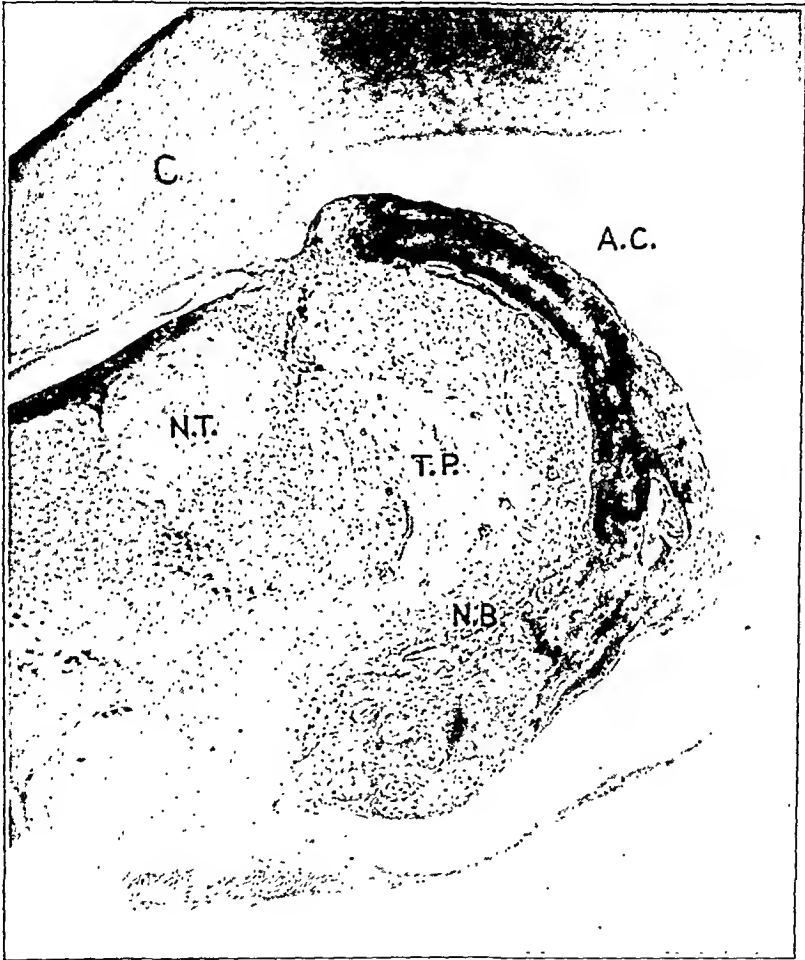


Fig. 5.—Higher power photomicrograph of a portion of the same transplant shown in figure 2. The transplanted segment of periosteum (*T.P.*) contains several areas of necrotic tissue and on its free edge a segment of anastomosing trabeculae of new bone. Designated also are the anterior chamber (*A.C.*) and the cornea (*C.*).

EXPERIMENT 3.—*Transplants of periosteum versus periosteum and bone salts.*

Comparative studies were made of thirty-three autogenous transplants of periosteum cultured in the eyes of twenty-one animals. Fifteen had been cultured in an aqueous humor containing bone salts, and the remaining eighteen were controls. New bone was found in twelve of the eighteen controls and in ten of the

fifteen specimens which were bathed in bone salts. New bone was found in specimens of both series when first examined ten days after transplantation, and in these and in specimens cultured at various periods up to one hundred and sixty-one days there was no demonstrable difference in the osteogenic activity or the quantity of newly formed bone. All transplants contained areas of necrotic tissue and pigmented cells, and a few had small encysted collections of salts.

EXPERIMENT 4.—*Transplants of boiled bone.*

In three rabbits autogenous transplants of small bits of bone removed from the tibias and boiled for a few minutes were made to the anterior chambers of each eye. Two eyes became grossly infected. A third transplant became attached to the cornea and apparently failed to establish a communication with vascular tissue, as indicated by the fact that it was entirely necrotic when examined sixty-five days after transplantation.

The other three transplants were attached to the iris and were cultured thirty-eight, sixty and sixty-five days, respectively. Histologic examination showed that all were necrotic but were undergoing absorption and invasion by granulation tissue which contained some pigmented cells, and in each specimen there was new bone in the fibrous tissue by which it was attached to the iris.

EXPERIMENT 5.—*Transplants of fascia versus fascia and bone salts.*

Fascia (autogenous) excised from the sheath of the rectus muscle was transplanted to the anterior chamber of each eye of fourteen rabbits. Into ten of the eyes bone salts were injected approximately ten days later. Microscopic examinations at periods varying from fifteen to one hundred and sixty days were made of eight specimens cultured in an aqueous humor containing bone salts and of thirteen in aqueous humor only.

All transplants were partially necrotic, and four were entirely so, three of them being apparently unattached to any tissue within the anterior chamber. Small particles of bone salts were encysted in the fibrous tissue, attaching the iris to the transplant in three of the specimens, but no specimen contained bone. There were many pigmented cells in the newly formed fibrous tissue.

EXPERIMENT 6.—*Transplants of mucosa of the urinary bladder alone versus the same plus bone salts.*

The urinary bladder was exposed in four rabbits, the serosa and muscularis teased from the mucosa and small pieces of this tissue excised, washed thoroughly in warm physiologic solution of sodium chloride and transplanted to the anterior chamber of each eye. Into three eyes bone salts were subsequently injected. Five specimens, two cultured in bone salts and three controls, were examined, one each at sixty-two days and the others at one hundred and eighty days. All contained epithelium characteristic of that lining the bladder. It was arranged in both single and multiple layers of cells which lined cysts containing a clear fluid stained faintly with eosin. There was also a submucosal layer of areolar tissue. No specimen, however, contained bone.

EXPERIMENT 7.—*Transplants of mucosa of the urinary bladder and fascia of the sheath of the rectus muscle versus the same tissues with the addition of bone salts.*

Eighteen rabbits with transplants of both mucosa of the urinary bladder and of fascia from the sheath of the rectus muscle in the anterior chamber of each eye provided twenty-four satisfactory specimens, eight of which had been cultured in a medium saturated with bone salts. The specimens were examined at periods varying from thirty-two to one hundred and sixty days after transplantation. Much of the fascia in each specimen was necrotic. Epithelium characteristic of

that lining the bladder (apparently very actively proliferating) was present in seven of the eight transplants cultured with bone salts and in fifteen of the sixteen controls. It had the same histologic characteristics as described in the preceding experiment. A photomicrograph of one specimen is illustrated in figure 6.

EXPERIMENT 8.—*Transplants of fascia plus bone ash.*

Bone ash was injected into the anterior chambers of seven eyes to which fascia from the sheath of the rectus muscle had been transplanted from eight to

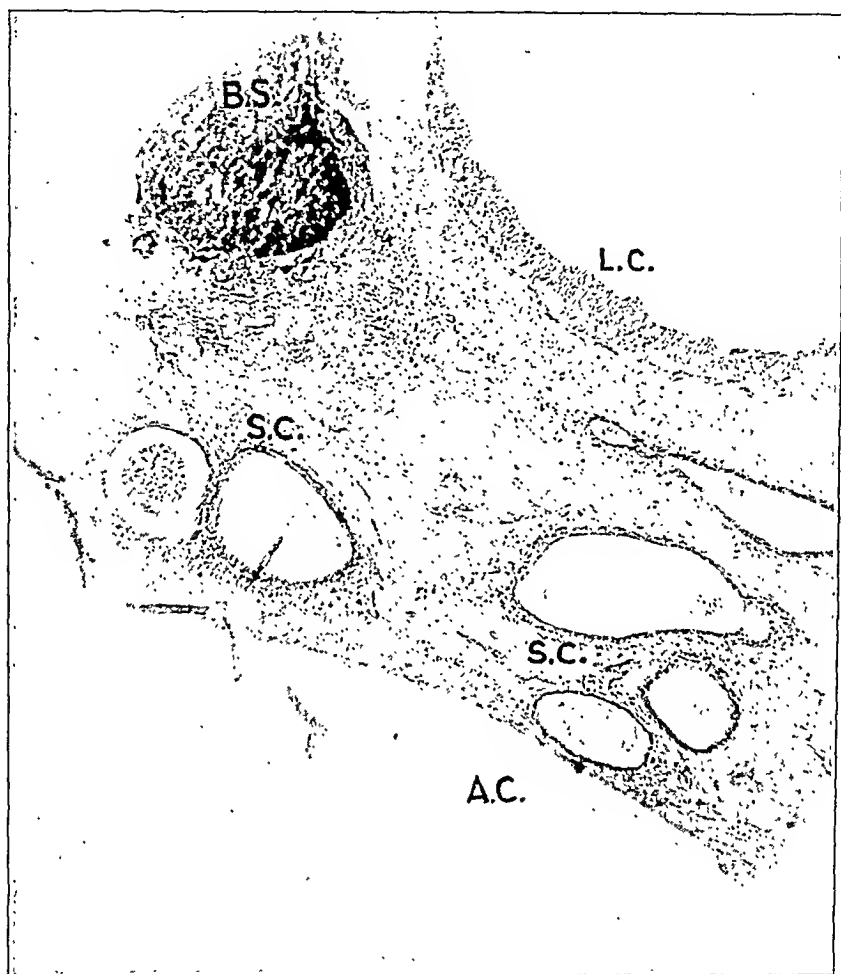


Fig. 6.—Photomicrograph of an autogenous transplant of mucosa of the urinary bladder and of fascia from the sheath of the rectus muscle in the anterior chamber of an eye of a rabbit one hundred and twenty days after transplantation. There is one large cyst (*L.C.*) and several small ones (*S.C.*) which are lined by stratified cuboidal epithelium (bladder) and contain fluid. Into the anterior chamber (*A.C.*) bone salts had been injected twice, some of which became encysted. There is no bone.

twelve days previously. The ash was obtained by baking large segments of the tibias of two rabbits in a furnace. In each instance the ash settled to the bottom of the anterior chamber and partially or completely surrounded the grafts. They were examined after twenty-six, forty-two, sixty-eight, eighty-two, one hundred

and twenty and one hundred and twenty-four days of culture. In each specimen there was much necrotic tissue, but in no specimen was there bone or calcified tissue. The granulation tissue contained many pigmented cells.

EXPERIMENT 9.—*Transplants of mucosa of the urinary bladder and fascia plus bone ash.*

Five transplants from five rabbits consisting of mucosa from the urinary bladder and fascia from the sheath of the rectus muscle were examined thirty-five, forty-eight, seventy, one hundred and twenty-two and one hundred and thirty days after

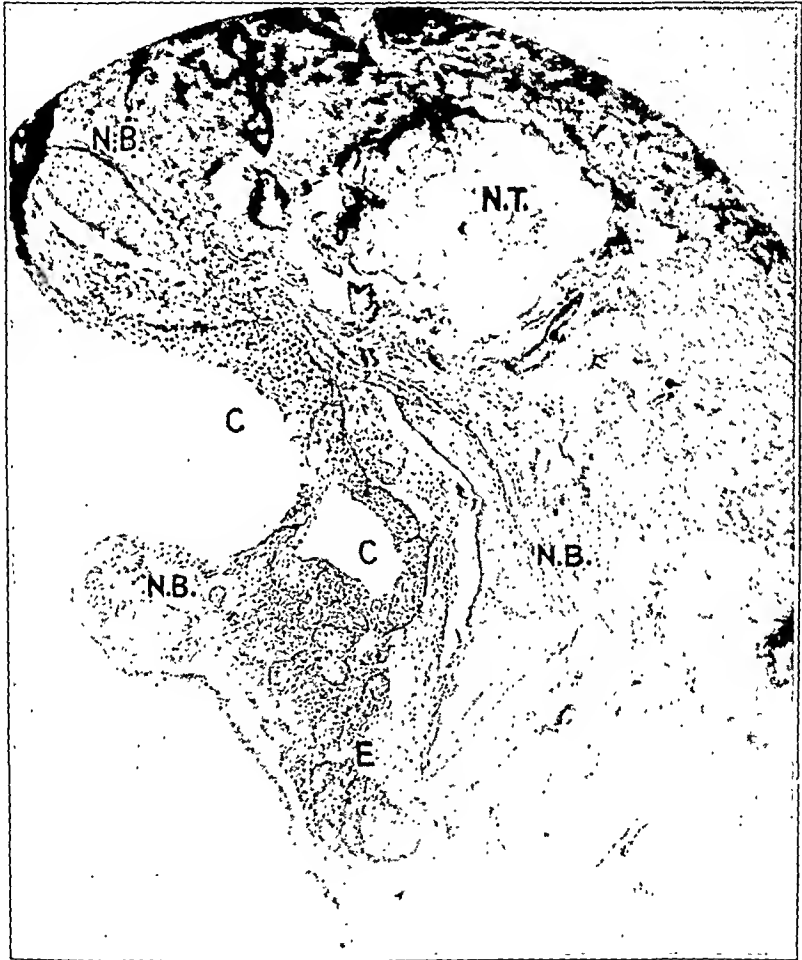


Fig. 7.—Photomicrograph of an autogenous transplant of mucosa of the urinary bladder and of fascia from the sheath of the rectus muscle in the anterior chamber of the eye of a rabbit one hundred and twenty-two days after transplantation. The transplanted tissue had been bathed in bone ash which had been injected into the anterior chamber twelve days after transplantation. As in figure 6, there are cysts lined with epithelium characteristic of that lining the bladder, but there is the important difference of the presence of plaques of new bone (N.B.) in the submucosal tissue. There are also solid cords of large epithelial cells (E.) and an area of necrotic tissue (N.T.).

transplantation. They had been cultured in the anterior chamber in an aqueous humor to which had been added sufficient bone ash to cover them completely.

In four of the five specimens there were many cysts lined with stratified cuboidal epithelium (of the type seen in the bladder) and areas containing these same cells arranged in solid cords. The transplanted fascia was partially necrotic. In two of these transplants, as illustrated in figure 7, there were plaques of new bone in the submucosal areolar tissue of the walls of several cysts, but in each instance it was confined to only a portion of the circumference of the cysts. The bone contained haversian canals and both fibrous and hematopoietic marrow.

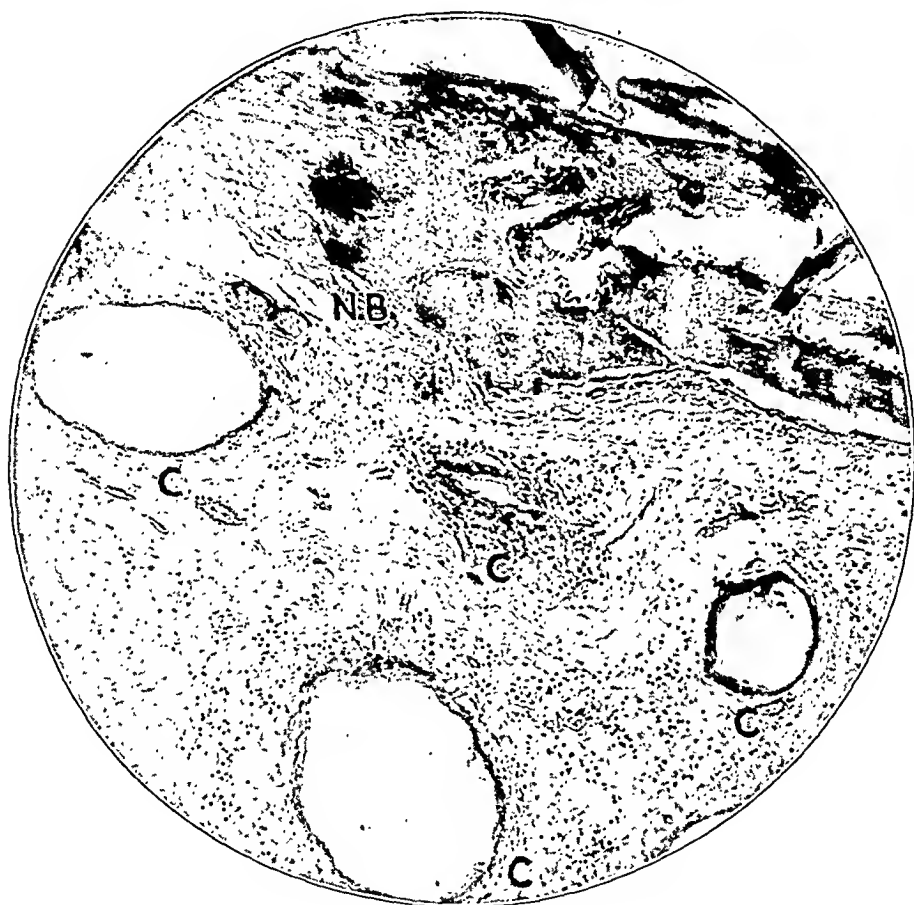


Fig. 8.—Photomicrograph of an autogenous transplant of mucosa of the urinary bladder and of fascia from the sheath of the rectus muscle in the anterior chamber of the eye of a dog. Note the cysts (C.) lined with epithelium characteristic of that lining the bladder and a mass of new bone (N.B.) in the submucosal fibrous tissue of a large cyst. Neither bone salts nor bone ash had been introduced into the eye.

EXPERIMENT 10.—*Transplants of mucosa of the urinary bladder and fascia of the sheath of rectus muscle.*

Transplants of the mucosa of the urinary bladder and fascia of the sheath of the rectus muscle to the eyes of three dogs yielded, seventy-two days after

transplantation, four satisfactory specimens, but only two contained epithelium characteristic of that lining the bladder. In each of these, however, there were epithelium-lined cysts, and in the walls of some of the cysts there were plaques of new bone. This bone contained haversian canals but only fibrous marrow. A photomicrograph of one specimen is illustrated in figure 8.

EXPERIMENT 11.—*Transplants of mucosa of the gallbladder and fascia of the sheath of the rectus muscle versus the same tissues with the addition of bone salts.*

In six rabbits there were placed into the anterior chambers of the eyes autogenous transplants of both mucosa of the gallbladder and of fascia from the sheath of the rectus muscle. Ten days later bone salts were injected into four eyes. The animals were killed thirty-two and seventy-five days later, and eight specimens were obtained for examination, consisting of four which had been cultured in aqueous saturated with bone salts and four controls. Two of the former and three of the latter specimens contained epithelium characteristic of that lining the gallbladder. In each instance the cells lined cysts, which were small and numerous. No specimen, however, contained bone. Much of the fascia was necrotic.

EXPERIMENT 12.—*Control rabbits.*

To determine whether trauma to the eye incident to the operative procedure necessary for the introduction of the transplants or whether the presence of the bone salts in the anterior chamber might in themselves induce osteogenesis in the tissues of the eye, these procedures were carried out, each in six rabbits. The eyes were examined both grossly and in serial microscopic sections at intervals ranging from sixteen to one hundred and seventy-six days. In a few instances bone salts were encysted in the iris, but in no specimen was bone found.

EXPERIMENT 13.—*Infection.*

Not infrequently bone has been found in human eyes in which there has been a panophthalmitis with subsequent recovery from infection and replacement of the necrotic tissue with fibrous tissue. As recorded in the report of the foregoing experiments, several rabbits acquired ophthalmitis in eyes in which the various transplants had been placed. Fourteen of these were carefully examined grossly, and all tissue with the consistency of bone was sectioned and studied microscopically. All had had the original infection more than one hundred and twenty days previously. In no specimen was bone found.

#### SUMMARY

In this group of experiments the anterior chambers of the eyes served as living culture tubes. In them tissues were cultured with direct vascular communications so that they received not only nutrition but also minerals, hormones, etc. By their vascular attachments they were suspended in a fluid which normally consists almost entirely of water. Its mineral content is negligible. Tissues cultured in this neutral medium served as controls for comparison with identical tissues cultured in aqueous surcharged with either bone salts or bone ash. Since the transplants contained necrotic tissue and were invaded by granulation tissue, there were present all the factors which the proponents of the chemical theory consider adequate for ossification, namely, a local surcharge of calcium, an active blood supply and fibroblasts.

Tissues known to be osteogenic, such as bone and periosteum, gave rise in each instance to new bone, and in comparing the control specimens with those cultured in bone salts no difference could be demonstrated in respect to the time of the beginning of ossification or in respect to the quantity or quality of the new bone. A much more luxuriant growth of bone formed from periosteum with which bone also had been transplanted than from transplants of periosteum alone.

Contrary to the observations of Key,<sup>4</sup> bone devitalized by boiling was found not to be inert. In the anterior chamber it gave rise to the formation of new bone in the surrounding fibrous tissue.

Fibrous tissue such as that present in the sheath of the rectus muscle failed to either calcify or ossify, regardless of the calcium content of the aqueous humor in which it was cultured.

It has been shown by Huggins<sup>7</sup> that the epithelium lining the urinary tract cultured in contact with certain types of fibrous tissue in vivo causes the deposition of bone in this fibrous tissue. Utilizing this contribution for the purposes of this problem, transplants consisting of epithelium from the bladder and fascia of the sheath of the rectus muscle were made into the anterior chambers of the eyes of both dogs and rabbits. In the dogs bone constantly developed in the submucosal fibrous tissue of the epithelial-lined cysts. None of the eyes of the dogs received bone salts. The same type of transplants in the rabbit cultured both with and without bone salts failed in each instance to produce bone. There developed only cysts lined with cuboidal epithelium. This distinction of behavior of transplanted epithelium from the bladder in the two types of animals was also observed by Huggins.<sup>7</sup>

However, in two of four transplants in rabbits in which the epithelium and fascia were cultured in mediums of aqueous containing bone ash, bone was deposited as in dogs in the fibrous tissue adjacent to the epithelium, which in many areas circumscribed fluid-filled cysts.

No bone was found in three series of eyes used as controls, namely, those into which bone salts only were injected, those subjected to operative trauma only and those in which infection had caused extensive destruction and fibrosis of the interior of the eyes. Only the latter group contained grafts.

#### CONCLUSIONS

The results of this investigation indicates that in experimental animals:

1. The synthetic salts of bone, calcium carbonate,  $\text{CaCO}_3$ , calcium phosphate,  $\text{Ca}_3(\text{PO}_4)_2$ , and magnesium phosphate,  $\text{Mg}_3(\text{PO}_4)_2$ , have no influence on osteogenesis or ossification. In great concentration and in the presence of tissue not in itself osteogenic but recognized as

ossifiable, these salts failed to give rise to the formation of bone, and in the presence of osteogenic tissue they appeared not to alter the normal course of ossification.

2. Bone, regardless of its viability, has a favorable influence on ossification. This was true of partially viable bone, boiled bone and bone ash. Transplants of the former invariably initiated ossification in the fibrous tissue surrounding them. This was also true of boiled bone, but to a much lesser degree, and although it did not occur with the use of bone ash under similar circumstances ossification did take place in transplants of fibrous tissue and epithelium from the bladder which were bathed in bone ash. Since bone was not formed in this type of transplant in the rabbit in mediums of either normal aqueous or bone salts, it is deduced that bone ash possesses some factor favorable to ossification which is not present in bone salts. It would seem likely, as suggested by Watt,<sup>16</sup> that calcium as it exists in bone exists in a physiochemical or structural form more suitable for use in the process of ossification.

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16. Watt, J. C.: The Deposition of Calcium Phosphate and Calcium Carbonate in Bone and in Areas of Calcification, *Arch. Surg.* **10**:983 (May) 1925.



# A PLAN FOR THE TREATMENT OF CANCER WITH SMALL QUANTITIES OF RADIUM

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A disease such as cancer, which is inevitably fatal if untreated, should receive the best possible management by physicians skilled in its diagnosis and treatment. The cancer institute is the ideal solution, as it includes a hospital organized and maintained solely for the diagnosis and treatment of cancer as well as adequate research laboratories. It is not feasible to care for all patients with cancer in institutes or hospitals devoted exclusively to the treatment of cancer because such institutions must be situated in centers of large population. It is obvious for economic and social reasons that the practical needs of the average community are best met by the cancer clinic in a general hospital. Since only a relatively small number of patients suffering from cancer can be taken care of in institutes and hospitals devoted to the treatment of cancer, the general hospitals throughout the country have the serious responsibility of caring for the greater proportion of patients with cancer. The organization of such a clinic has been described in a previous article.<sup>1</sup>

In addition to facilities for roentgen diagnosis, it is essential that the tumor clinic in a general hospital be supplied with a high voltage x-ray machine of sufficient voltage to insure effective external irradiation. Such a therapeutic unit should have a peak strength of 200,000 volts, which is the standard for most therapeutic x-ray machines in the United States today. The machine may be air cooled or water cooled at from 20 to 30 milliamperes; the latter set-up is more economical and time saving, particularly when there are many patients to be treated.

## THE DISTRIBUTION OF RADIUM

At the Memorial Hospital many requests have been received for information concerning the amount of radium necessary for effective radium therapy in a general hospital or in private practice and the proper distribution of this radium in various applicators. Many visitors

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From the Memorial Hospital for Cancer and Allied Diseases, New York, and the Josephine Lendrim Tumor Clinic of the Paterson General Hospital, Paterson, N. J.

1. Pack, G. T.: The Organization of a Tumor Clinic in a General Hospital, Surg., Gynec. & Obst. 58:248-254, 1934.

to this institution either are engaged to some extent in the treatment of cancer or contemplate the organization of a clinic for this purpose. They not only are interested in the routine diagnostic and therapeutic measures at the Memorial Hospital but seek to apply this information to their own needs. They see in daily use almost 4 Gm. of radium in solution in an emanation plant, another 4 Gm. in a radium element pack for external irradiation, a battery of high voltage x-ray machines, a General Electric x-ray unit operating at from 700,000 to 1,000,000 volts, a Heublein teleroentgenotherapeutic unit for diffuse irradiation to the entire body at from 10 to 12 feet (305 to 365 cm.), skin plaques, trays and vaginal bombs with values of from 1,000 to 2,000 millicuries and gold radon seeds in abundance for every need. The diagnostic pro-

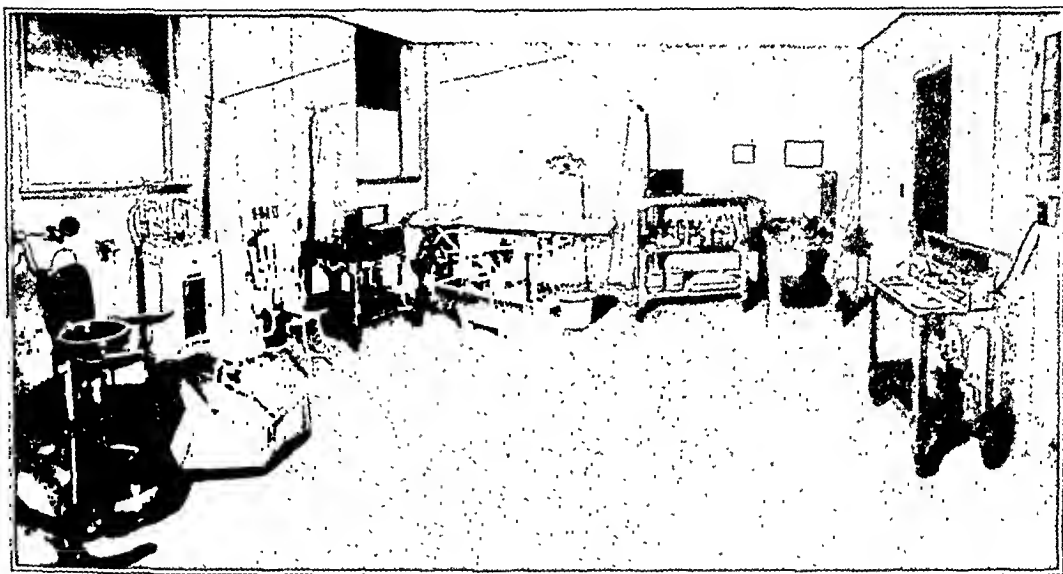


Fig. 1.—Diagnostic and therapeutic unit of a tumor clinic.

cedures and the surgical principles employed at this institution are readily utilized elsewhere, but the technic of radiation therapy may not be at all practical or suitable for general hospitals or tumor clinics in smaller communities, where such equipment is seldom available. The interns graduating from the six months' service at the Memorial Hospital and even the clinical fellows on completion of their three year course experience great difficulty in their new locations with the limited quantities of radium usually available, the form of applicators in which the radium is disposed, the new technical methods of treating cancer with a small amount of radium and the cost of gold radon seeds when purchased elsewhere.

What is the minimal quantity of radium necessary for a tumor clinic? How should the radium be distributed among the various applicators? What is the approximate cost of the radium and the equipment for its use? These problems are very important at this time, when so many new cancer clinics are being organized throughout the United States. No arbiter dares to specify the absolutely minimal number of milligrams of radium essential for all hospitals. The purchaser must consider such data as the population of the city, the death rate from cancer in the city, the estimated number of cases of cancer in the community, the number of beds in the hospital housing the tumor clinic, the proportion of patients with cancer in the past experience of the hospital and the prospective rate of growth of the tumor clinic and its future needs. I am not championing small quantities of radium against a larger supply, as I believe that every tumor clinic should own as much radium as possible. If a gram of radium is owned, it may be best to place it in solution in an emanation plant (approximate cost \$6,000) and employ radon rather than radium element. If greater quantities of radium are available (2 Gm. or more), a radium element pack in a permanent fixed applicator may be used for external irradiation (telerradium therapy) in lieu of or supplementary to high voltage roentgen rays. The radium element (i. e., radium salt) is the form generally found suitable for amounts of less than 500 mg.

The quantity of radium should be sufficient to care for all cancers, but there should not be any in excess of this amount, as idle radium is too expensive. The radium may be purchased in such a flexible arrangement that the entire amount can be used interchangeably in the breast, uterus, mouth or skin. The radium may be arranged in such a distribution that additional milligrams may be added to the supply from time to time without disturbing the general scheme, the technic or the type of radium applicators. I can best illustrate these points by citing the experience of the Josephine Lendrim Tumor Clinic of the Paterson General Hospital in Paterson, N. J. This general hospital, with a capacity of 325 beds, is located in a city of approximately 150,000 inhabitants. Five years ago, through the generosity of Mr. Hugh Lendrim, I was given *carte blanche* in organizing this tumor clinic and planning the distribution of radium and the equipment for its application. The plan was so successful that later I introduced it into the tumor clinics of the Yale School of Medicine and the College of Medicine of Ohio State University.

The radium salt is distributed in individual platinum cells, measuring 11.5 mm. in length, 1 mm. in external diameter and 0.2 mm. in wall thickness. These individual radium cells were first employed by Sluys of Belgium. I introduced them into the United States five years ago

and have constructed this plan of radium therapy around these units. The radium content of each cell is either 1.33 mg. (delivering 10 microcuries destroyed hourly) or 3.33 mg. (delivering 25 microcuries destroyed hourly). The quantity of radium might be 2 and 5 mg., a distribution that is more common in the United States, but the expression of dosage by the Continental notation of "millicuries destroyed" for interstitial irradiation is more quickly arrived at by using the former plan. The platinum cells of uniform size and shape are kept in a specially designed container, which affords filtration and protection. The number of these cells, containing a total quantity of 130 mg. of radium, and the various applicators in which they are used are summarized with specifications in one of the following tabulations.

The radiologist seldom has occasion to use more than 130 mg. of radium in the treatment of any one cancer, provided supplementary high voltage x-rays are available. These platinum cells containing radium may be used without additional filtration on superficial lesions of the skin or in wax moulages for irradiation of cancer of the lip, or all these cells (totaling 77) may be grouped together in any of the various skin plaques or trays. Furthermore, they may be placed in special applicators for irradiation of the vagina or in a bomb for radium therapy of the uterine cervix. The volume of these seventy-seven tiny cells is quite small. The individual cells may be transferred to platinum capsules for esophageal or intra-uterine use or for employment in Curie colpostats, the capsules giving the additional filtration that is necessary for these locations. If interstitial irradiation is contemplated, the cells may be placed in hollow sheath needles with removable trocar points. These needles are available in various lengths and will hold one, two or four cells placed end to end. If a carcinoma of the tongue is to be irradiated interstitially, the short needles are loaded with single cells. If the next patient is to receive interstitial radium therapy for a carcinoma of the breast, the cells are transferred to the longer sheath needles, which will hold four cells.

This flexible distribution enables the clinic to obtain the greatest use of a small quantity of radium. It is an economical plan as it avoids a large initial expenditure for radium and keeps the radium constantly in use. It is obviously cheaper to buy various radium applicators, unfilled sheath needles and other supplies in quantity than it is to purchase an inflexible distribution of radium permanently arranged in capsules and needles of different lengths. For example, many radiologists have radium in quantities of 25 and 50 mg. in separate capsules for intra-uterine treatment; these fixed applicators are not suitable for intra-oral irradiation. Radium is also supplied in the form

of fixed needles which may be grouped and screened for use in the uterus, but on the whole this arrangement is not as convenient as the one just described.

In the following pages I shall describe briefly the principles and practice of radium therapy in a tumor clinic in a general hospital, realizing at the same time that these statements summarily given are dogmatic and often controversial. The technic of therapy to be given later for cancers of various locations is not necessarily what I consider



Fig. 2.—Closet enclosing built-in radium safe and cabinet for case histories.

to be ideal. For example, gold radon seeds are preferable in my opinion to radium needles for interstitial irradiation of cancers of the urinary bladder and oral cavity. The methods described in this article are based on the best utilization of a small quantity of radium element as used in tumor clinics in general hospitals. *The description is not a summary of the technic in use at the Memorial Hospital.*

The following tabulations present information concerning the equipment and distribution of radium for a cancer clinic.

*Specifications for Radium (130 Mg.) and Containers for Tumor Clinic, with  
Estimate of Cost*

All the radium is furnished in platinum cells 11.5 mm. in length, 1 mm. in external diameter and 0.2 mm. in wall thickness.

No. of Cells	Radium Content per Cell	Total No. of Mg.	Value
14	3.33 mg.	46.62	\$1,631.70
63	1.33 mg.	83.79	2,932.65
		<hr/>	<hr/>
		130.41	\$4,564.35
14	Platinum cells. (The 14 cells containing 3.33 mg. are each gold-plated to distinguish them from the 63 cells containing 1.33 mg. each), at \$4.00 each.....		\$ 56.00
63	Platinum cells, at \$3.25 each.....		204.75
6	Platinum-iridium tubes with bulldog eye, measuring 19.53 mm. in external length, 3.87 mm. in external diameter, and 0.3 mm. in wall thickness, each to contain 4 of the foregoing cells, at \$20.00 each..		120.00
1	Platinum-iridium tube with bulldog eye, measuring 19.5 mm. in external length, 4.13 mm. in external diameter and 12 mm. in internal length, to contain 8 cells.....		23.00
3	Special screw cap brass tubes of 1.5 mm. in wall thickness, 24 mm. in external length, 7 mm. in external diameter, 20 mm. in internal length and 4 mm. in internal diameter, at \$2.50 each.....		7.50
10	Small platinum-iridium (20 per cent) needles with one eyelet and removable trocar point (Treves needles), measuring 17 mm. in length, 1.65 mm. in external diameter and 0.3 mm. in wall thickness. Each to hold 1 cell at \$10.00 each.....		100.00
14	One cell gold sheath needles with removable platinum-iridium points, at \$4.80 each.....		67.20
8	Two cell gold sheath needles with removable platinum-iridium points, at \$5.40 each.....		43.20
12	Four cell gold sheath needles with removable platinum-iridium points, at \$6.45 each.....		77.40
3	Brass plaques of varied sizes to hold the radium cells in the treatment of epithelioma of the skin, at \$10.00.....		30.00
1	Tray or pack—distance applicator for radium. Designed to contain the platinum-filtered radium cells.....		18.00
10	Curie colpostats, at \$0.85 each.....		8.50
1	Flat vaginal applicator or spoon (Hcaly model).....		18.00
1	Bomb for surface irradiation of cervix (Bailey model).....		25.00
1	Berven tonsil applicator for surface irradiation of tonsil.....		45.00
1	Intubation tube (O'Dwyer model) for larynx. Designed to hold radium cells within its circular walls.....		20.00
	Equipment for protection of radium workers.....		250.00
Total .....			<hr/> \$5,677.90

It is suggested that a quantity of 250 mg. of radium, employing the removable platinum cell technic, be divided as follows:

1	Platinum-iridium tube containing a platinum cell permanently sealed in the tube, which has a bulldog eyelet. The over-all length of the tube is 21.7 mm.; the wall thickness, 0.5 mm. of platinum; the external diameter, 2.5 mm. This tube costs \$20.00 and contains 26.64 mg. of radium (200 microcuries destroyed hourly) ..	26.64 mg.
4	Platinum-iridium tubes each containing a platinum cell permanently sealed in the tube. The over-all length of the tube is 21.7 mm.; the wall thickness, 0.5 mm. of platinum; external diameter, 1.9 mm. Each tube costs \$12.75 and contains 13.32 mg. of radium (100 microcuries destroyed hourly) .....	53.28 mg.
51	Platinum cells, 11.5 mm. long with a wall thickness of 0.2 mm. of platinum, each to contain 3.33 mg. of radium .....	169.83 mg.
Total .....		249.75 mg.

The tubes containing 26.64 and 13.32 mg. of radium are to be used for uterine irradiation, the 26.64 mg. tube being used for the cervix and one 13.32 mg. tube within the body of the uterus proper, the remaining three 13.32 mg. tubes in a Curie colpostat furnishing a proper combination for radium therapy of cancer of the cervix. A different arrangement is employed for carcinoma of the body of the uterus. The individual platinum cells are for the needles, tubes, plaques and moulages of various types.

#### *Cost of Equipment for Protection of Radium Workers*

Assembly table with lead shield .....	\$150.00
This table is devised to afford adequate protection to the worker who assembles the radium applicators. It is 32 inches (81.2 cm.) high, 48 inches (121.9 cm.) long and weighs 770 pounds (349.6 Kg.). It is readily portable owing to its mounting on four roller-bearing casters. A lead shield 13 inches (33 cm.) wide, 22 inches (55.8 cm.) high, 3 $\frac{3}{8}$ inches (8 cm.) thick and weighing 550 pounds (249.7 Kg.) is erected at one end of the table. At the top of the shield is an adjustable lead glass plate to protect the eyes (design by Failla).	
Assembly forceps with lead hand shield .....	20.00
The forceps for handling radium has a cup-shaped lead shield on its handle to protect the fingers from exposure to radiation.	
Hand carrier for radium or radium applicators .....	40.00
A radium carrier, such as has been designed by Failla for use in the Memorial Hospital, is absolutely necessary to transport the radium and radium applicators. It is essentially a cylinder 7 inches (17 cm.) in diameter and 4 inches (10.2 cm.) deep, with a wall of lead of $\frac{1}{2}$ inch (1.27 cm.) thickness, enclosed in a monel case. A handle 15 inches (38 cm.) in length supplements the protection afforded by the heavy filtration. The top closes automatically while it is carried.	

Container for individual platinum cells of radium..... 40.00

When not in use the platinum cells containing the radium are kept in a lead box container made of hinged lead plates 1 inch (2.5 cm.) thick. Seventy-seven small countersunk holes are of sufficient size and depth to hold the platinum cells. In this arrangement the radium is constantly visible, the loss of a single cell is at once detected and the cells are easily grasped and removed when it is necessary to assemble the various applicators.

The specifications for the sheath needles are given in table 1.

TABLE 1.—*Specifications for Sheath Needles*

To Accommodate	Total Length, Mm.	Internal Length, Mm.	External Diameter, Mm.	Internal Diameter, Mm.	Wall Thickness, Mm.
1 cell (Treves needle).....	17.0	12.0	1.65	1.05	0.3 (platinum-iridium)
1 cell (gold sheath type).....	24.5	12.0	1.9	1.1	0.4 (gold)
2 cells (end to end).....	36.0	23.5	1.9	1.1	0.4 (gold)
3 cells (end to end).....	47.5	35.0	1.9	1.1	0.4 (gold)
4 cells (end to end).....	59.0	46.5	1.9	1.1	0.5 (gold)

The 0.4 mm. wall thickness of the gold sheath needles is equivalent to 0.3 mm. of platinum. The combined wall thickness of the gold sheath needle and the 0.2 mm. platinum cell is equivalent to 0.5 mm. of platinum.

The Treves radium needle <sup>2</sup> is a tiny single cell needle which is very serviceable in the interstitial irradiation of intra-oral cancers because of its small size. Platinum with 20 per cent iridium is used. The over-all length of the needle is 17 mm., the internal diameter 1.05 mm., the wall thickness 0.3 mm. and the external diameter 1.65 mm., which are the smallest dimensions of any interstitial radium applicator with the exception of the radon seed. The tip has a removable trocar point 2 mm. in length for the insertion of the cell into the needle. There is a space of 12 mm. in the bore of the needle to contain the platinum-radium cell. The total filtration of needle and cell is 0.5 mm. of platinum.

#### NOTATION OF DOSAGE

In America the dosage is expressed in terms of milligram hours or millicurie hours, which is a constant value, being the dose of emission of radium. It is computed by multiplying the intensity of the radiation (i. e., quantity: milligrams of radium element or millicuries of radium emanation) by the duration in hours of the application. The notation used throughout France makes the dose proportional to the quantity of radon destroyed during its application. This notation (Debiegne and

2. Treves, N.: A Small Platinum Needle Designed for the Use of Various Strengths of Radium Element Interstitially, *Am. J. Roentgenol.* **33**:537-544, 1933.



Regaud, 1914; Regaud and Ferroux, 1919) is preferable because it is equally applicable to radium or radon and for expressing doses of external and interstitial radiation. Let it be assumed that the total therapeutic value of 1 millicurie of radium emanation is 133 millicurie hours. Therefore, 1 millicurie destroyed is the equivalent of 133 millicurie hours or of 133 milligram hours, or 1 milligram of radium acting for one hundred and thirty-three hours may be expressed in terms of dosage as 1 millicurie destroyed. One millicurie destroyed is equal to 1,000 microcuries destroyed. The radium element is distributed in platinum cells, each containing 3.33 or 1.33 mg. of radium, which give radiations equaling 25 and 10 microcuries destroyed hourly.

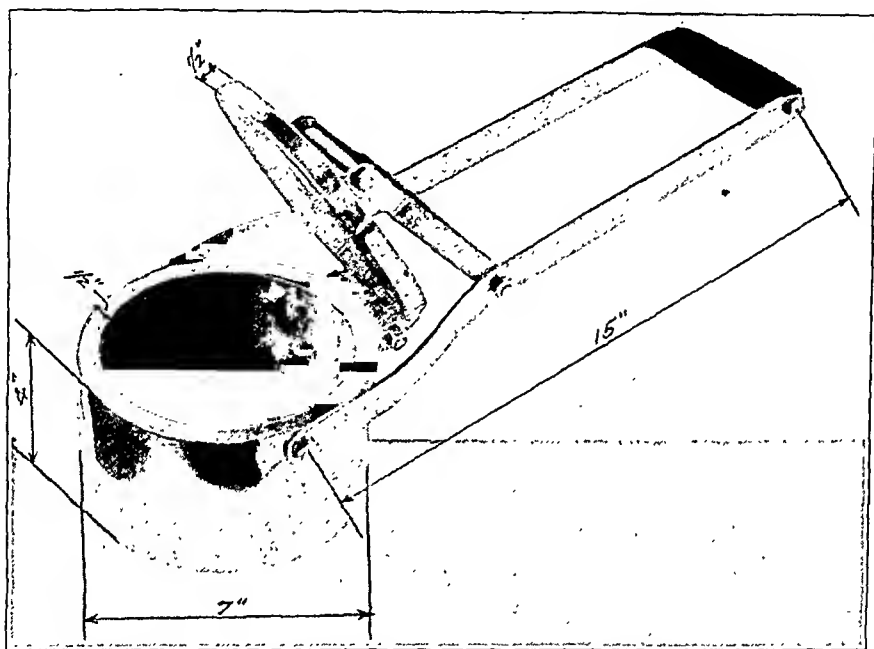


Fig. 3.—Radium carrier in a monel case, lead filled. The position of the handle determines the opening and closing of the lid. Protection is afforded not only by the heavy filtration of the walls but by the long handle (Failla model).

#### THE TIME-INTENSITY FACTOR

Some criticism has been leveled at this plan for radium therapy, because of the small quantity of radium available for any one treatment, i. e., the low intensity and long duration of such treatments. In fact, this is an advantage rather than a handicap, because the modern trend is to apply smaller quantities of radium for a longer time (within limits). At the Radium Institute of the University of Paris, where 9 gm. of radium is available, the use of capsules in the uterus and needles in the

tongue is favored. Both the capsules and the needles are of low radium content, and several days is required to deliver a cancerocidal dose. By such methods the radiotherapist may safely give a much larger total dose than would be possible with a greater intensity. My associates and I<sup>3</sup> have given abundant experimental proof to substantiate this theory in a previous article.

It seems logical to assume that a cancer cell or a tissue cell would not be indifferent to variations in the intensity of radiation. Such a cell, continuously engaged in self-repair, the ingestion, consumption and stor-

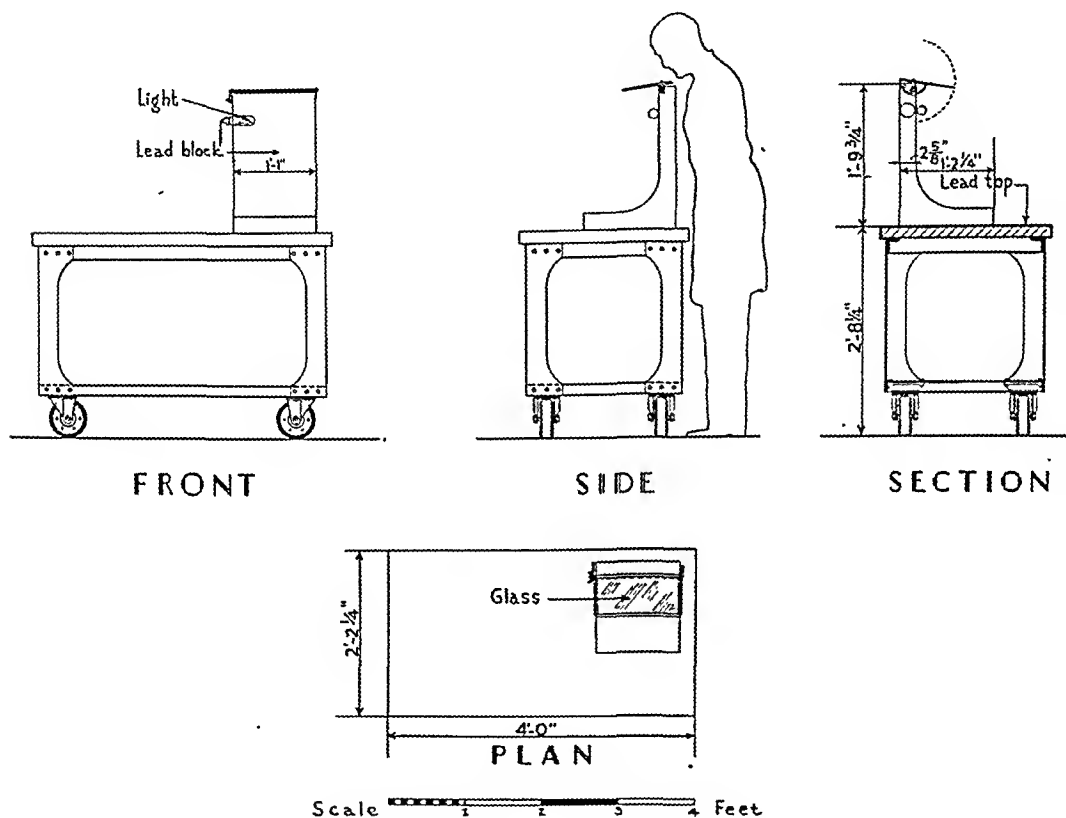


Fig. 4.—Diagram and plan of the radium assembly table.

age of food, the excretion of waste products, the pursuit of its specific function and possible preparation for cell division, and in delicate ionic balance with the tissue juices which bathe it, is a living unit and must be capable of making certain adjustments to the influences of noxious agents to which it is exposed, whether they are chemical or physical. All physiologic processes require time for their completion. If the doses were equal, the cell—either normal tissue cell or cancer cell—should be

3. Pack, G. T., and Quimby, E. H.: The Time-Intensity Factor in Irradiation, *Am. J. Roentgenol.* 28:650-666, 1932.



and the preservation of normal tissue cells; there is clinical and experimental evidence to suggest that long duration and low intensity of irradiation (within limits) have greater differential effects on tumor cells than on normal tissue cells.

Interstitial irradiation, even though more intense, may produce differential effects according to the intensity and duration of irradiation. Radon deposited interstitially has an exponential rate of decay, less than 1 per cent remaining at the end of thirty days. The irradiation by this interstitial method is therefore continuous but with diminishing intensity. There is some question concerning the relative effectiveness of continuous irradiation by radon with an exponential diminution in intensity or by radium element interstitially with a constant equal intensity and the same total dose. For all these reasons I am inclined to prefer a low intensity of constant radium value, even though this may require from

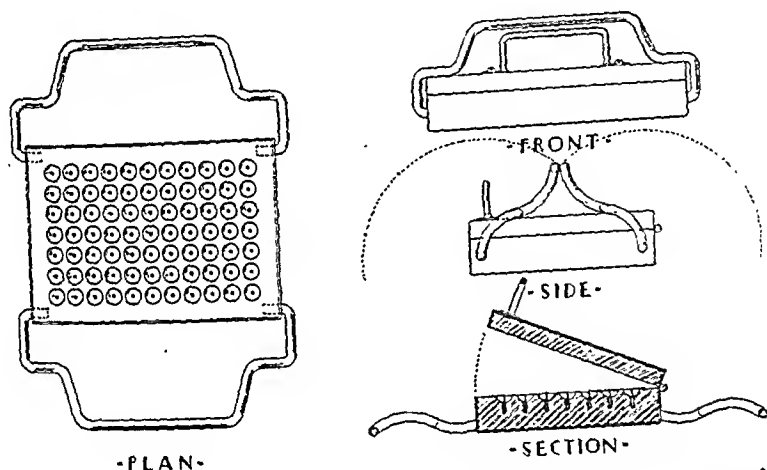


Fig. 6.—Permanent radium container for platinum cells. A monel box is lead filled to afford greater protection by filtration. Each platinum cell is in its individual counter-sunk hole, so that one may see at a glance whether or not all the cells are present. The arrangement requires less handling of the radium. A detachable long handle is provided to use for carrying.

five to ten days of continuous application (exclusive of preliminary external irradiation) in the case of cancer of the uterus and of the tongue.

#### RAPID CALCULATION OF RADIUM DOSAGE AND TIME OF EXPOSURE

Friedman of the New Haven Hospital, where this method is in daily use, has devised a slide rule which simplifies the calculation of exposure.<sup>4</sup>

4. Friedman, Irving: A Slide-Rule for Calculating Radiation Exposure When Cells of Uniform Radium Content Are Used, *Radiology* 2:365-366, 1934.

On one side is a scale of logarithmic form, to compute the duration of exposure required in order to administer a desired amount of radiation with a given number of cells. On the other side is a scale of linear form, to determine the time of day when the exposure should be terminated.

The operation of this device can be explained by the following illustrative example (fig. 9): Suppose that a dose of 2,200 milligram

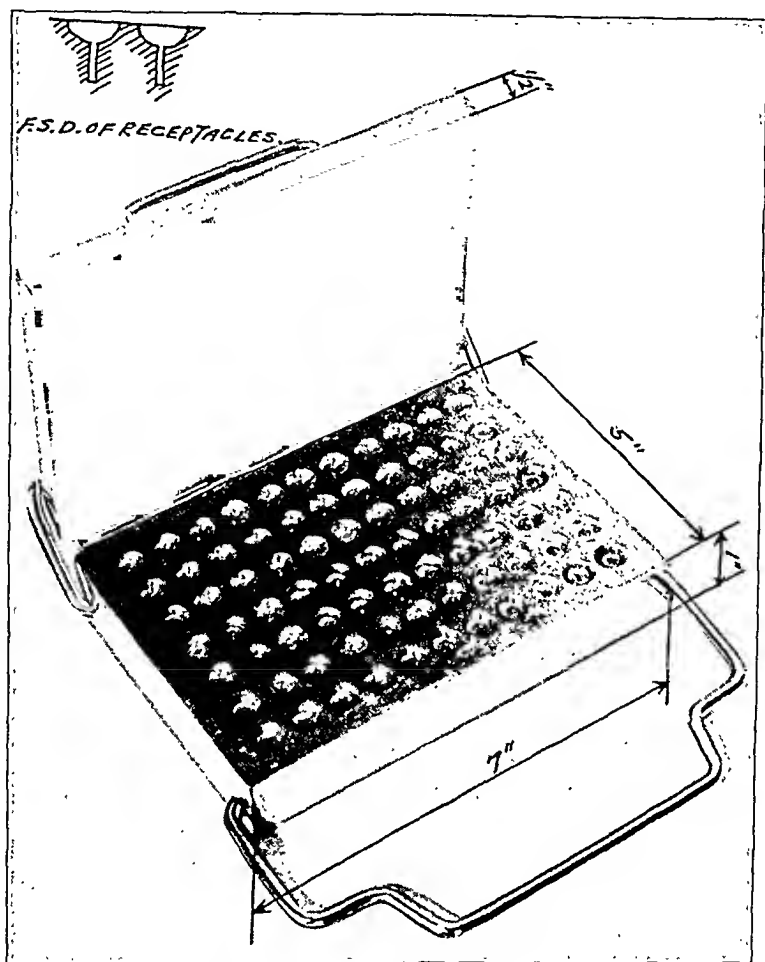


Fig. 7.—Radium container for platinum cells, in a monel case, lead filled.

hours (approximately 16.5 millicuries destroyed) is to be delivered to a cancer of the tongue and that eight needles, each containing 3.33 mg. of radium in a single cell, are required. The first sliding scale is adjusted so that the indicator points to 2,200 milligram hours of radiation. The required exposure is then read on the lowermost scale opposite 8, the number of cells, which in this case would be approximately eighty-three hours. The rule is then turned over, and the second sliding scale is

adjusted so that one of the two indicators points to 8 p. m., the hour the needles were inserted. From this it may be seen that the treatment is terminated at 7 a. m. of the fourth day, the day being read on the same side as the indicator which marks the beginning of the exposure. This rule is accurate to within a small fraction of 1 per cent.

#### CALCULATION OF DOSAGE

It is necessary to know and to plan the quantity of irradiation to be delivered to any tumor. As it is technically impossible to irradiate any tumor absolutely homogeneously, the radiotherapeutist adopts as the delivered or tissue dose the minimal quantity of radiation received at any point in the tumor; the rest of the tumor must therefore receive more than enough if the minimal dose delivered has the capacity of sterilizing the cancer. The tissue dose in the tumor is then of more importance than the applicator dose or dose of emission, because the latter notations do not indicate the quantity of radiation actually delivered into the tumor. These are best expressed in terms of biologic

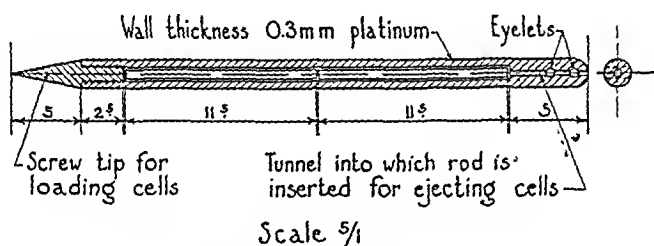


Fig. 8.—Diagram of a sheath needle designed to hold two removable radium cells.

units; such a unit is the threshold erythema dose used at the Memorial Hospital and is defined as that dose which in 80 per cent of the cases produces a faint reddening or bronzing of the skin in from ten to twenty days and in the other 20 per cent produces no visible effect. This threshold skin erythema dose may be the biologic unit for all tissue doses, whether delivered by external or by interstitial irradiation.

All radiation applicators, external, interstitial and intracavitary, are calibrated by this common biologic unit, so that the tissue dose can be estimated at all depths below the surface of the skin and in tumors of all dimensions. This technic has been the work of Quimby and is outlined in summary here. The applicator dose necessary to produce the threshold erythema dose is found by direct experimentation; then the percentage of the amount falling on the skin, which reaches various depths, is determined by means of a water phantom and small ionization chamber. The tissue dose delivered in the tumor by external irradiation is considered as the dose delivered at that point which lies deepest or at

the greatest distance from the skin portal.<sup>5</sup> The tissue dose can be calculated properly only when the primary tumor and its metastases are measured in all diameters; the exact depth from skin portals must also be recorded. The calculation of tissue dosage for interstitial irradiation is based on the practice of considering all tumor masses as lying just within a sphere or composed of two or more adjacent or overlapping spheres, each of which is treated individually in the case of long narrow tumors (Martin and Quimby). Quimby has devised a table giving the quantities of radiation from interstitial sources necessary to deliver specified minimum threshold erythema doses in various spherical volumes (table 2). This table is invaluable to the clinical radiotherapist, as it

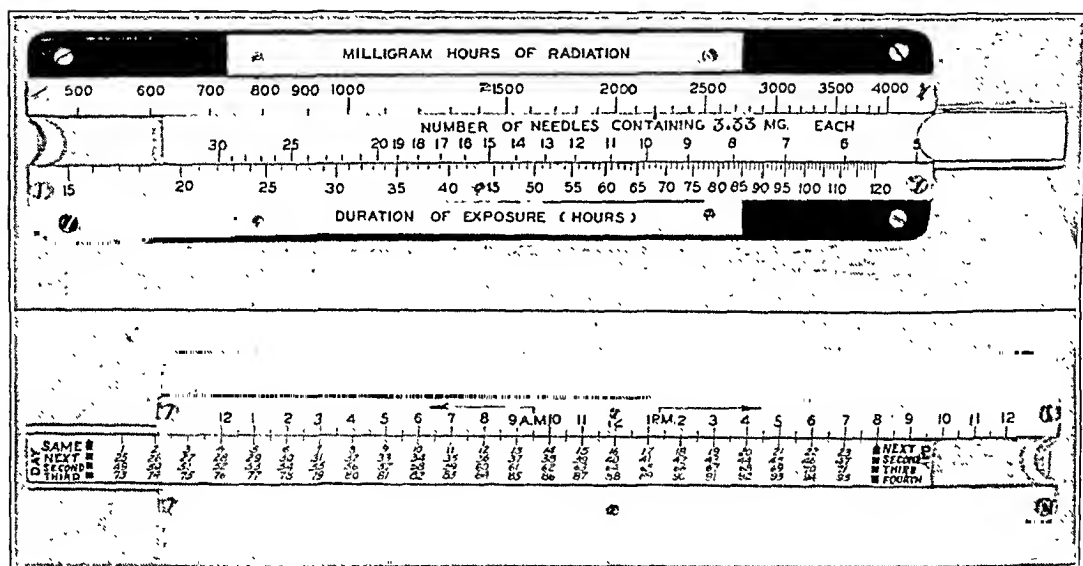


Fig. 9.—A slide rule for the rapid calculation of dosage of radium and time of exposure. The logarithmic and linear forms are based on the platinum cell as a unit, each to contain 3.33 mg. of radium.

enables him at a glance to know the exact quantity of interstitial radiation necessary to deliver any desired tissue dose in a tumor of any size.<sup>6</sup>

Clinical experiments with cancers of the mouth, breast, bladder, skin, rectum, stomach and prostate have demonstrated that the lethal tissue dose for malignant tumors of these organs varies from 3 to 10 threshold erythema doses, depending on the radiosensitivity and on other factors. A specific example of the applicability of this method may be worth

5. Martin, H. E.; Quimby, E. H., and Pack, G. T.: Calculations of Tissue Dosage in Radiation Therapy, *Am. J. Roentgenol.* **25**:490-506, 1931.

6. Quimby, E. H.: Physical Factors in Interstitial Radium Therapy, *Am. J. Roentgenol.* **33**:306-316, 1935.

while here.<sup>7</sup> A mammary carcinoma with a volume of 60 cc. has already received a total of 3 threshold erythema doses from fractionated high voltage x-rays cross-firing through two ports. A total tissue dose of 7 threshold erythema doses is required, so that the rest (7—3 threshold erythema doses), or 4 threshold erythema doses, must be given by interstitial methods. According to table 2, this would be 4,550 milligram hours, or 34 millicuries destroyed. This dose is then administered by the insertion of radium element needles. The dosage table is strictly applicable only for radium needles to be left in place four days or longer; when the time of irradiation is less, allowance is made by decreasing the quantity of radiation used.<sup>8</sup>

Quimby employed radium needles of various lengths (0.5 mm. platinum filter) in detailed experiments on rabbit muscle and butter

TABLE 2.—Quantities of Radiation from Interstitial Sources Necessary to Deliver Specified Minimum Doses in Various Volumes\*

Threshold Erythema Doses	Volume, Cc.										
	10	20	30	40	60	80	100	125	150	200	250
	Millicurie, or Milligram Hours										
1	275	380	470	530	650	750	845	955	1,060	1,250	1,410
2	550	760	940	1,060	1,300	1,500	1,690	1,910	2,120	2,500	2,830
3	825	1,140	1,410	1,590	1,950	2,250	2,535	2,865	3,180	3,750	4,240
4	1,100	1,520	1,880	2,120	2,600	3,000	3,380	3,820	4,240	5,000	5,660
5	1,375	1,900	2,350	2,650	3,250	3,750	4,225	4,775	5,300	6,250	7,070
7	1,925	2,660	3,400	3,710	4,550	5,250	5,915	6,685	7,420	8,750	9,900
10	2,750	3,800	4,700	5,300	6,500	7,500	8,450	9,550	10,600	12,500	14,100
	Millicuries Destroyed										
1	2.1	2.9	3.5	4.0	4.9	5.6	6.4	7.2	8.0	9.4	10.6
2	4.2	5.8	7.0	8.0	9.8	11	13	14	16	19	21
3	6.3	8.7	10.5	12	15	17	19	22	24	28	32
4	8.4	12	14	16	20	22	26	29	32	38	42
5	10.5	14	18	20	24	28	32	36	40	47	53
7	15	20	24	28	34	39	45	50	56	66	74
10	21	29	35	40	49	56	64	72	80	94	106

\* These doses are for needles to be left in place four days or longer. If they are to be removed in two or three days, all quantities of radiation should be about 10 per cent less. A platinum filter of from 0.3 to 0.5 mm. was used.

decoloration and from these studies formulated certain rules which are important whenever linear radium foci are to be used interstitially. Distances of from 1.5 to 2 cm. are recommended as the proper spacing of the needles in a single parallel series.<sup>9</sup> For two series in parallel planes, she advised that the needles should never be placed farther apart than the distance between the planes, and even closer spacing may be

7. Lee, B. J., and Pack, G. T.: Tissue Dosage Estimation in Mammary Cancer, Bull. Memorial Hosp., New York 1:67-73, 1929.

8. Quimby, E. H.: Determination of Dosage for Long Radium or Radon Needles, Am. J. Roentgenol. 31:74-91, 1934.

9. Quimby, E. H., and Stewart, F. W.: Comparison of Various Sources of Interstitial Radiation, Radiology 17:449-470, 1931. Quimby, E. H.: A Comparison of Radium and Radon Needles and Permanent Radon Implants, Am. J. Roentgenol. 23:49-56, 1930.



advantageous. The needles are of such length that the active radium-bearing portions extend completely beyond the limits of the tumor. In practice, the volume of tumor irradiated is considerably larger than the actual measurements of the tumor. The periphery of the lesion should receive a heavily concentrated dose, as it is most needed at the growing edge of the tumor. If the radium needles are placed more widely apart, the dose per needle or per centimeter of needle length must be much greater than when they are close together. Such intense doses may lead to radionecrosis around each needle. The length of the implant has also been given consideration by Quimby. For a given number of millicurie or milligram hours, the longer the radium needle the shorter the distance at which a given dose is delivered by the needle, or conversely, the greater the amount of radiation necessary to deliver 1 threshold erythema dose at a given distance. The quantities of radiation necessary to deliver 1 threshold erythema dose at a distance of 1 cm. for radium needles of various lengths, each with a 0.5 mm. platinum filter, are given in Quimby's table (table 3). These facts are fundamentally essential in the employment of the radium needles described in this text.

TABLE 3.—*Quantities of Radiation Necessary to Deliver 1 Threshold Erythema Dose at 1 Cm. from Needles of Various Lengths \**

Length of Needle, Cm.	Quantity of Radiation	
	Millicuries or Milligram Hours	Millicuries Destroyed
0.5.....	115	0.85
1.0.....	130	1.00
1.5.....	144	1.1
2.0.....	158	1.2
3.0.....	186	1.4
4.0.....	220	1.6
6.0.....	285	2.1
8.0.....	370	2.8
10.0.....	475	3.6

\* A platinum filter of 0.5 mm. was used.

#### RENTAL OF RADIUM FOR MAINTENANCE OF CLINIC

It is not the purpose of this article to present any plan for financing a tumor clinic. The Josephine Lendrim Clinic of the Paterson General Hospital as well as certain other tumor clinics in general hospitals are sufficiently endowed to care for all indigent patients who apply but cannot pay for treatments. The complete facilities of the clinic are tendered to all patients with cancer, regardless of their financial status. For those who can pay, a small registration fee is collected at the first visit, and a small charge is made for subsequent dressings, when this is necessary. Because of the many inquiries received concerning the rental rates of radium, I am presenting herewith a scale of prices used in the Josephine Lendrim Clinic, realizing at the same time that these

charges, while flexible, may not be suitable for clinics in other communities. The patients applying to the tumor clinic are classified by the social secretary into four groups, based on an appraisal of their financial status. These are as follows: *A*, private patients; *B*, semiprivate patients; *C*, clinic patients and *D*, special patients who cannot afford the regular rates. The charges are made for each 1,000 milligram hours consumed and are subdivided according to the following plan:

Grade of Patient	A	B	C	D
Rate per 1,000 milligram hours.....	\$20.00	\$10.00	\$ 5.00	\$3.00
Minimal charge.....	40.00	20.00	10.00	5.00

On this basis, a semiprivate patient who receives 3,000 milligram hours of radium will pay the hospital \$30. A clinic patient who receives 1,500 milligram hours of radium therapy will pay the hospital the minimal charge of \$10. The money so obtained is used solely for the maintenance of the clinic.

#### TREATMENT OF CANCER

*Epithelioma of the Skin.*—This superficial and accessible cancer may be treated successfully by any one of a number of methods of radiation. A careful observance of the response of this type of tumor to radium and roentgen therapy affords a good object lesson in the technical details and physical principles involved. In the majority of cases cancer of the skin may be cured by low voltage roentgen therapy, very light filtration or no filtration being employed. Unlike cancer of other regions, epithelioma of the skin is usually treated by a single application of radium or x-rays. The same methods, principles and dosage are applicable to squamous cell carcinoma and to basal cell carcinoma of the skin, provided the size and degree of infiltration are equal. The basal cell epithelioma is a relatively radiosensitive lesion, except when bone or cartilage is invaded; the development of adenoid features indicates a greater radioresistance.

In lieu of the individual moulages which are used for radium treatment in particular cases, the tumor clinic may find a series of plaques suitable for the majority of epitheliomas of the skin. These plaques have different dimensions for their radiating surfaces, but all have the same filter and are applied at a distance of 1 cm. They are modifications of the applicators designed at the Memorial Hospital by Dr. Failla. A small plaque, 1.8 cm. square, has a radiation surface of 2 sq. cm. The floor, or filter, of the plaque is a 2 mm. plate of brass, to which should be added the 0.2 mm. of platinum for the radium-bearing cells which fit into the brass plaque. A similar plaque, rectangular and measuring 2.7 by 1.7 cm. in diameter, has a radiating surface of 3.75 sq. cm. A larger

round plaque with a diameter of 4 cm. and a radiating surface of 7 sq. cm. is also useful in the treatment of lesions of greater dimensions. The interiors of these boxlike plaques are subdivided into loges devised to hold the radium cells. The radium-skin distance is constantly 1 cm., and this distance is obtained by the intervention of blocks of balsa wood 1 cm. in thickness. The dose varies from 700 milligram hours in the case of the small, square plaque to as high as 2,000 milligram hours for the larger, round plaque (fig. 10).

The radium tray is a small external applicator for radium therapy; the radium is applied in it at a distance of 3 cm. from the skin. The

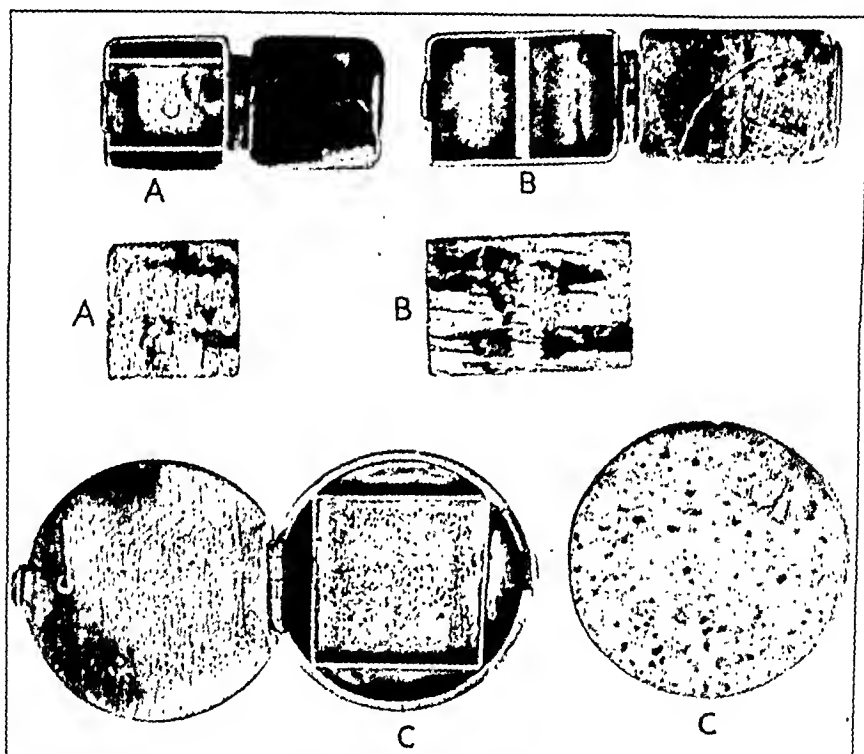


Fig. 10.—Plaque containers for superficial radium therapy of cancer of the skin. The compartments are of the proper size to contain the platinum cells of radium. All of the cells may be placed in any one of these plaques. The three models (*A*, square plaque; *B*, long or rectangular plaque, and *C*, round plaque) are shown with their respective blocks of balsa wood (1 cm. thick) used to give the proper radium-skin distance.

filter is also 2 mm. of brass, which is supplemented by the filtration strength of the radium cell, i. e., 0.2 mm. of platinum. The distance is obtained by a circular box or short cylinder, on the top of which is an especially designed tray or radium container. The interior of this tray is grooved by a serrated comb, by means of which the radium cells are distributed properly over the surface. On top of this is placed an addi-

tional small compartment for odd radium tubes. The radium tray gives a greater depth dose than the small radium plaques and is therefore useful in the treatment of the carcinoma of considerable depth, such as the recurrent mammary carcinoma in the skin or tumors of the parotid glands (fig. 11).

If the tumor projects to any considerable height above the surface of the skin, the quantity of radiation necessary to sterilize the base of the tumor can be materially lessened by removal of the superficial portion by endothermy. The focal distance of the radium from the skin depends on the size and the type of the lesion to be treated. The deeply

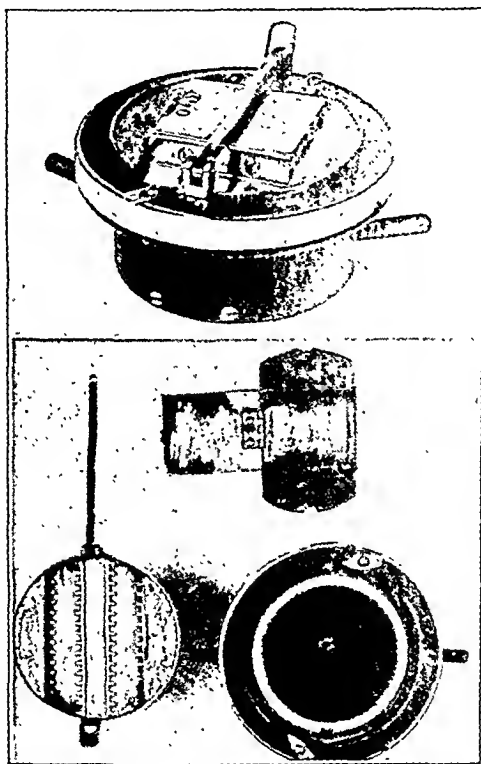


Fig. 11.—Radium tray for use at 3 cm. distance from the skin. The instrument is photographed assembled and disassembled to show the arrangement for the platinum radium cells. The accessory small brass box on the cover is for supplementary radium.

infiltrating carcinoma and the carcinoma with a large surface dimension require an application of radium at greater distances than is necessary for the small superficial epithelioma. This distance is obtained in many cases, particularly for the epithelioma of irregular outline and on uneven skin surface, by the intervention of a wax which is transparent to the gamma rays of radium. The formula for this wax is 100 Gm. of yellow wax, 100 Gm. of paraffin fusible at 62 C. and 20 Gm. of finely

sifted sawdust. This mixture is melted into sheets 1 cm. thick. It softens readily at 48 C. and is molded over the tumor until it hardens into a permanent moulage. The mixture can be sterilized at 120 C. and used again. It is said that this wax has approximately the same absorption coefficient as the skin. It is also maintained that, unlike dental modeling compound, it does not give off many secondary beta rays during the permeation by the gamma rays. If the cancer of the skin is small and flat, the focal distance may be only 0.6 cm., but if it is elevated or a large lesion, the distance is correspondingly greater, as from 1 to 1.5 cm.<sup>10</sup>

In general, the dose per unit of surface is increased with the thickness of the intervening wax (radium-skin distance), augmented with the thickness of the filter and diminished with the extent of the surface irradiated, without mentioning the influence exercised on the estimation of the dosage by biologic factors, such as differences in radiosensitivity. Regardless of the histologic grading of the carcinoma, the dose selected is usually the one capable of sterilizing the most radio-resistant epidermoid carcinoma, with preservation of the normal tissues. This dose varies from 0.8 to 5 millicuries destroyed (from 100 to 650 milligram hours) per square centimeter of surface irradiated; e. g., for a small epidermoid carcinoma, such as one 2 sq. cm. in area, the dose may be 4.5 millicuries destroyed per square centimeter of tumor, but for a larger carcinoma, such as one 25 sq. cm. in area, the dose may be only 2 millicuries destroyed (266 milligram hours) per square centimeter of tumor.<sup>11</sup>

Occasionally the radiotherapist must employ interstitial irradiation for the larger, deeply infiltrating epithelioma of the skin. The small single cell needles are inserted in a radial or grid distribution through and beneath the tumor, the points of insertion being immediately peripheral to the margin of the tumor. The needles may thus be anchored to normal skin and are not easily dislodged. The dose depends on the estimated cubic content of the epithelioma and may be derived from table 4.

*Malignant Melanoma.*—The treatment for the malignant melanoma is wide, radical surgical excision, preferably with the endotherm knife. The tumor should be handled with extreme gentleness during its removal. Frank E. Adair and I have studied over four hundred cases of this type of tumor at the Memorial Hospital and found only seven—

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10. Pack, G. T.: Radium Therapy of Tumors of the Skin at the Curie Institute of the University of Paris, Arch. Dermat. & Syph. **18**:286-289 (Aug.) 1928.

11. Pack, G. T.: Radiation Therapy of Cancers of the Orbitopalpebral Region at the Radium Institute of the University of Paris, Arch. Ophth. **57**:246-253 (May) 1928.

teen in which the growth exhibited any appreciable response to irradiation. Radiation therapy alone is not sufficient to control the growth and metastasis of this tumor, nor is it of prophylactic value in the treatment of the regional lymph node areas. In the treatment of melanoma of the extremities I am committed to prophylactic inguinal or axillary dissection, reserving radiation therapy for postoperative use in order to induce firm scarring and possible imprisonment of residual melanoma cells (abortive fibrosis).

*Neurogenic Sarcoma.*—In the majority of cases of neurosarcomas the neoplasm is radioresistant. The several factors which militate against successful radiation therapy are: first, the inherent radioresistance of the disease, even the very cellular neurosarcoma; second, the location of the tumor in regions which will not tolerate intensive irradiation well; third, the poor vascular supply to the tumor, which with its density accounts for frequent ulceration and radionecrosis after treatment, and fourth, the multicentric origin of the tumor. Cure has been obtained in a few cases by interstitial irradiation, needles containing

TABLE 4.—*Radium Applicators for Epitheliomas of Skin\**

Type	Size	Area Radiating Surface, Sq. Cm.	Radium Skin Distance, Cm.	Dose in Milligram Hours
Square plaque.....	1.8 cm. square	2.0	1	700-800
Long plaque.....	2.7 cm. by 1.7 cm.	3.75	1	1,000-1,200
Round plaque.....	4 cm. in diameter	7.0	1	1,400-1,600
Tray.....	6.2 cm. in diameter	17.5	3	3,000-3,500

\* The filter used for all types was 2 mm. of brass and 0.2 mm. of platinum.

one, two or four platinum cells being used in tandem. In other cases a neurosarcoma has regressed with external irradiation alone; this response is not rapid, as in most malignant tumors, but is a slow, progressive diminution in size, due apparently to the conversion of the tumor into a fibrotic mass. The treatment of choice continues to be wide surgical excision and avulsion of the involved nerve, if identified, followed by heavy external irradiation. In some cases, particularly those of recurrent tumor, amputation is necessary.

*Cancer of the Lip.*—Cancer of the lip is irradiated from three sides by the surface application of a wax moulage in which the radium cells are implanted. The wax is either the wax described earlier in this paper or dental modeling compound. The size and shape of the epithelioma are cast in the moulage (fig. 12). The small radium cells are then embedded in the inner surface of the moulage corresponding to the site of the epithelioma and a surrounding area from 1 to 1.5 cm. The focal distance thus obtained is approximately 0.5 cm. and is determined by the thickness of the intervening wax. The filter used is

only 0.2 mm. of platinum. Each platinum-filtered radium cell used to deliver the dose contains 3.33 mg. of radium, which gives off 25 microcuries destroyed hourly. The average dose is from 0.75 to 1 millicurie destroyed (133 milligram hours) for every square centimeter of tissue treated. This dose varies according to the surface dimensions and the depth of infiltration of the carcinoma. The time of application is from eighteen to thirty-six hours. If the carcinoma infiltrates the lip deeply, it may be necessary to resort to interstitial irradiation, in which case the Treves platinum-filtered needles, each containing one radium cell, are inserted in parallel arrangement through the vermilion border of the lip deep into the substance of the tumor. Although radium has largely supplanted surgical intervention in the treatment of labial epi-

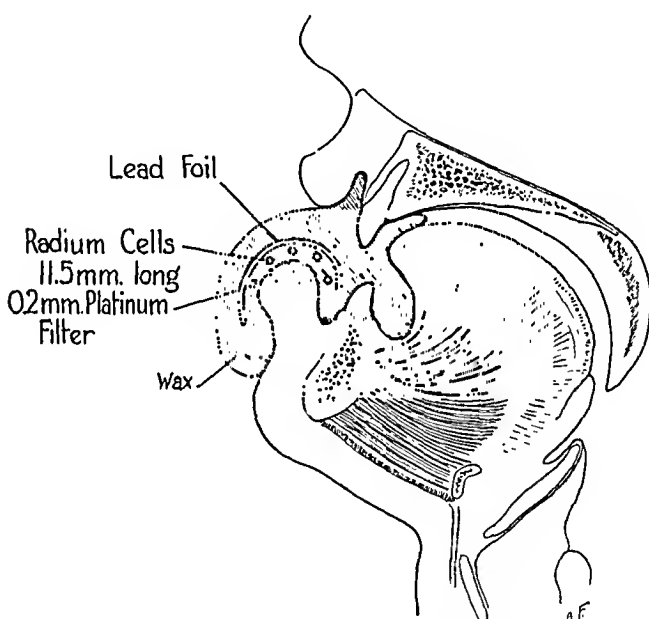


Fig. 12.—Moulage of wax or dental modeling compound used in the radium treatment of carcinoma of the lip.

thelioma, extensive surgical excision of the lower lip with plastic closure must be resorted to for (a) bulky, fungating infected carcinoma, (b) local recurrence after incomplete surgical excision and (c) local recurrence after inadequate irradiation. The methods of cheiloplasty employed are modifications of the operations of Bernard and Estlander devised by Hayes Martin.

*Cancer of the Tongue.*—The comparative malignancy and radiosensitivity of lingual cancer in various locations ascend in the following order: dorsolingual anterior cancer < infralingual cancer < dorsolingual posterior cancer. The papillary cancer is less malignant than the ulcerative, infiltrative cancer in the same location. In most instances

the epidermoid carcinoma of the mouth is not more radioresistant than the epidermis from which it is derived and generally it is less radioresistant. The dosage for sterilization of cancer of the lip, mouth or pharynx is from 75 to 100 per cent of the epidermicidal dose.<sup>12</sup> As computed experimentally with the use of gold radon seeds, this dose is approximately 8 threshold erythema doses.<sup>5</sup> This figure cannot be applied exactly to the dose delivered by radium needles, as the radiation here is linear in distribution rather than a point source, as in the case of the gold radon seed. For practical purposes, however, the dose delivered by radium needles is only slightly less than that employed with gold radon seeds.

In the treatment of cancer of the tongue the teeth are thoroughly cleansed, pyorrhea is treated and the necessary dental extractions are performed before radiation therapy is started. The mouth is cleansed by daily irrigations with saline solution or a solution of potassium permanganate during the course of treatment. While radioactive foci are within the mouth, the radium-bearing tissue is surrounded by a lead-filtered wax moulage held in place by the teeth and protecting the remainder of the mouth from the injurious and unpleasant effects of diffuse radiation.

The hollow needles employed for interstitial radium therapy of cancer of the tongue and of the floor of the mouth are of three sizes. Small platinum-iridium needles have been designed by Norman E. Treves which are admirably suited for the treatment of a small cancer in the floor of the mouth or in the lip, cheek, tonsil or palate; each needle holds one platinum cell of radium and has one eyelet and a removable trocar point. It is only 17 mm. in length and has a wall thickness of 0.3 mm., which, with the inner platinum cell, affords a total filtration of 0.5 mm. of platinum. Other hollow needles are of gold sheath design and contain one or two platinum-filtered radium cells (end to end). They are of similar design but somewhat longer, measuring 24.5 and 36 mm., respectively, with internal lengths (true linear focus of radium) of 12 and 23.5 mm. The total filtration when ready for use is the equivalent of 0.5 mm. of platinum. These needles are more suitable for use in the tongue. The true focus, i. e., the length of the needle occupied by the radium, is such that it will give a cylinder of irradiated tissue rather than a sphere, as obtains with the use of radon seeds (fig. 13).

Regional anesthesia is used, and the needles are introduced into the tongue and completely buried there. Each gold sheath needle has a

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12. Regaud, C.: On Curietherapy of the Epitheliomata of the Tongue and of Their Following Adenopathy. *Brit. J. Radiol. (B. A. R. P. Sect.)* **30**:351-357, 1925.



double eye; the lower eye is for suturing the needle with silk thread to the neighboring lingual tissue; the upper eye is for external anchorage by means of a heavy thread which passes out of the mouth. It is important that the buried needles are parallel with each other. Furthermore, the needles must be a distance of 1 cm. or more apart from each other in order to prevent possible necrosis from too intense radiation and from secondary rays flying from adjacent needles.

Ordinarily about one-half as many platinum cells of radium are employed in the interstitial treatment of oral cancer as there are millicuries destroyed in the total dose; e. g., if the total dose is to be 20

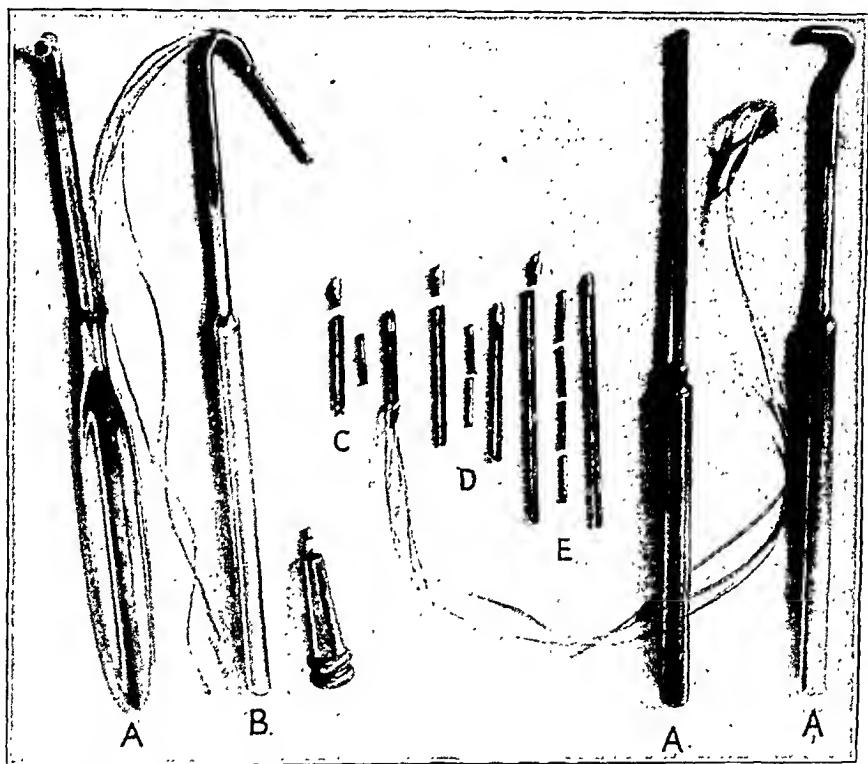


Fig. 13.—*A* are types of angled insertors for radium needles. *B* is an insertor with threaded radium needle attached; *C*, assembled and dissembled sheath needle designed to contain one platinum filtered radium cell; *D*, a sheath needle for two radium cells to be used in tandem formation, and *E*, a sheath needle for four radium cells.

millicuries destroyed, ten needles holding one cell of radium each are used. Occasionally long needles containing two cells of radium (end to end) are employed in the tongue, in which case correspondingly fewer needles are needed. These needles must sometimes remain in situ for as long as five days in order to deliver the required dose. The optimal dose per unit volume of tumor has been estimated approxi-

mately at 130 millicurie hours per cubic centimeter of tissue. This amount of radiation is sufficient to cause a marked reaction in the tumor and its environment but not enough to induce radionecrosis (fig. 14).

Radium therapy is of palliative benefit for cancer of the mouth in an advanced stage, but in such cases one cannot safely use the same rules as when a less advanced state of the disease permits an attempt at cure. In the intentionally palliative treatments, large doses are avoided and moderate successive irradiations are preferred to a single intense one.

The principles established by Regaud for the treatment of intra-oral cancer are closely followed. These are summarized briefly as follows: (1) the distribution of numerous and weak radioactive foci in the cancer and surrounding tissue, care being taken to create a radia-

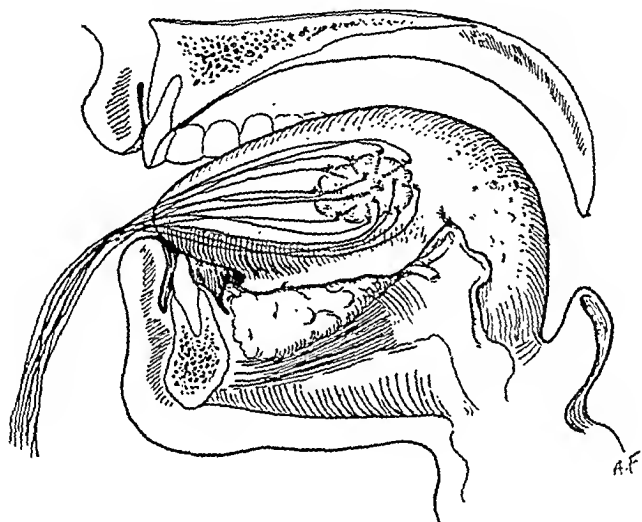


Fig. 14.—Method of interstitial radium therapy of lingual cancer. Each needle has two threads in double eyelets, one for suture and anchorage to adjacent normal tongue and the other to extend out of the mouth for fixation to the cheek.

tion field as homogeneous as possible; (2) the use of the gamma rays only in order to avoid a necrotizing effect; (3) continuous irradiation of low intensity for a long time, and (4) the use of a single treatment for successful results, as a carcinoma acquires radioresistance from prolonged and improperly spaced repeated irradiations.<sup>12</sup>

Cancer of the lateral, anterior or dorsal surfaces of the tongue is readily treated by the previously mentioned procedures because of its accessibility. Interstitial radium therapy is superior to the surgical extirpation of such a cancer. A cancer situated on the posterior aspect of the tongue is difficult to treat because of its position; this same handicap obtains for surgical intervention even when the cancer in this location is small. Some of these lesions descend deeply into the

pharynx and hypopharynx and are poorly treated by radium puncture alone. Supplementary external irradiation is always given over the superior part of the neck prior to interstitial irradiation of the cancer in this location. Angled needle insertors are helpful in the treatment of cancer of the posterior part of the tongue. Cancer in this location and involving the valleculae may require supplementary interstitial irradiation; the radium needles may be inserted into the base of the tongue through the floor of the mouth anteriorly or through the submental or suprahyoid region, under the guidance of a directing finger at the base of the tongue.<sup>13</sup>

Cancer of the infralingual region and of the floor of the mouth, even when tiny, is seldom cured by surgical removal. If the cancer infiltrates deeply into the muscles of the tongue, interstitial irradiation of the infiltrating tumor must be carried out; however, there are certain dangers attendant on the interstitial irradiation of cancer in this location. Radium therapy of the floor of the mouth frequently causes radionecrosis; another dangerous complication is the occasional development of a phlegmon in the submental region. Superficial papillary carcinoma of the floor of the mouth may be treated satisfactorily by topical surface irradiation. For suitable cases an apparatus in the nature of a wax moulage is molded directly and applied to the floor of the mouth, bringing the radium cells in close approximation to the tumor and its environment. The tongue is protected by a lead shield during this treatment. Interstitial irradiation is occasionally contraindicated, if the cancer involves the mucous membrane covering the inferior maxilla. Carcinoma of the superior or the inferior alveolus is treated by the application of radium on a mold; if this is unsuccessful, the maxilla is resected and the site later irradiated by external radium therapy. After the direct irradiation of the floor of the mouth has been completed, or even prior to this in certain cases in which there is infection, the submental region is irradiated by means of high voltage x-rays, cross-fired through both submaxillary regions to concentrate on the floor of the mouth. The submaxillary and submental lymph nodes thus receive prophylactic irradiation, although this is of questionable curative value. If the lymph nodes are already palpable, the external irradiation is either preceded by neck dissection or followed by interstitial irradiation.

*Malignant Tumor of the Tonsil.*—A tonsillar neoplasm in most instances is radiosensitive and is managed well by external irradiation alone. The tonsil, tonsillar pillars, soft palate, pyriform sinuses and base of the tongue constitute Waldeyer's ring, a common site for such

13. Pack, G. T.: The Management of Intra-Oral Cancers at the Radium Institute of the University of Paris, *Ann. Surg.* 90:15-25, 1929.

extremely radiosensitive tumors, such as the lympho-epithelioma and the transitional cell carcinoma. Even an epidermoid carcinoma in this location is usually anaplastic and labile to the effects of radium and x-rays. Tonsillectomy is always contraindicated.

The factors used in the sterilization of a tonsillar tumor by means of x-rays are: 200 kilovolts, 30 milliamperes, a target-skin distance of 60 cm. and a filter of 0.5 mm. copper and 2.5 mm. aluminum. Two lateral portals are used, the beams being directed through metal cones containing diaphragms and cross-fired through each posterior portion of the cheek and the upper part of the neck. A total dose of from 3,200 to 4,000 roentgens is given to each side by the fractionated method, with only 300 roentgens daily, alternating to each side of the neck. Three weeks is needed in which to deliver this dose.

Interstitial irradiation is seldom employed for tonsillar carcinoma unless the lesion does not show the usual response to well planned roentgen therapy; it must be employed cautiously because of the danger of late radionecrosis and hemorrhage from overdosage. The combination of external and interstitial irradiation is more practical and safer when the dose of x-rays is limited to from 1,200 to 1,500 roentgens. The small Treves single cell needles are most satisfactory for this purpose; each needle is loaded with a cell containing either 3.33 or 1.33 mg. of radium. I have found that the optimal dose per needle should not exceed 1.5 millicuries destroyed (200 milligram hours).

The Berven tonsil applicator is an excellent instrument for the topical application of radium to the tonsillar region.<sup>14</sup> This apparatus consists of a dental plate for fixation against the teeth, a pivot-joined piece, the pivots of which fit into the notches of the dental plate and allow movement round a vertical axis, an interlocking hook, a cylindric inner blade of the forceps at the end of which is a radium plate, and an outer blade of the forceps with a pad for pressure against the outside of the cheek. When this instrument is assembled as shown in figure 15, it may be applied to either the right or the left tonsil. The dose and method of treatment are the same as outlined by Berven in his monograph. Atropine sulfate,  $\frac{1}{150}$  grain (0.4 mg.), is given hypodermically thirty minutes before the treatment is started. The pharynx is anesthetized by swabbing with a 10 per cent solution of cocaine. Soft warm dental modeling compound is tied on the radium plate, and an impression is made of the region to be treated. After the moulage is cold and firm, the platinum cells, each containing 3.33 mg. of radium, are embedded at a distance of from 0.4 to 0.6 cm. below the surface. As many of these cells as possible are placed side by side within the

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14. Berven, Elis G. E.: Malignant Tumors of the Tonsil. *Acta radiol., supp.* 11, 1931, pp. 1-285.

wax, and the surface is covered with a thin coat of paraffin. The total dose given is from 500 to 1,000 milligram hours. A suitable lead foil protection is affixed to the posterior side of the radium plate. Dental modeling compound is also placed in the dental plate which holds the jaws together when compression is made by the teeth. An outside screw is used to adjust the pressure of the radium applicator against the tonsil and the counterpressure of the outside plate against the

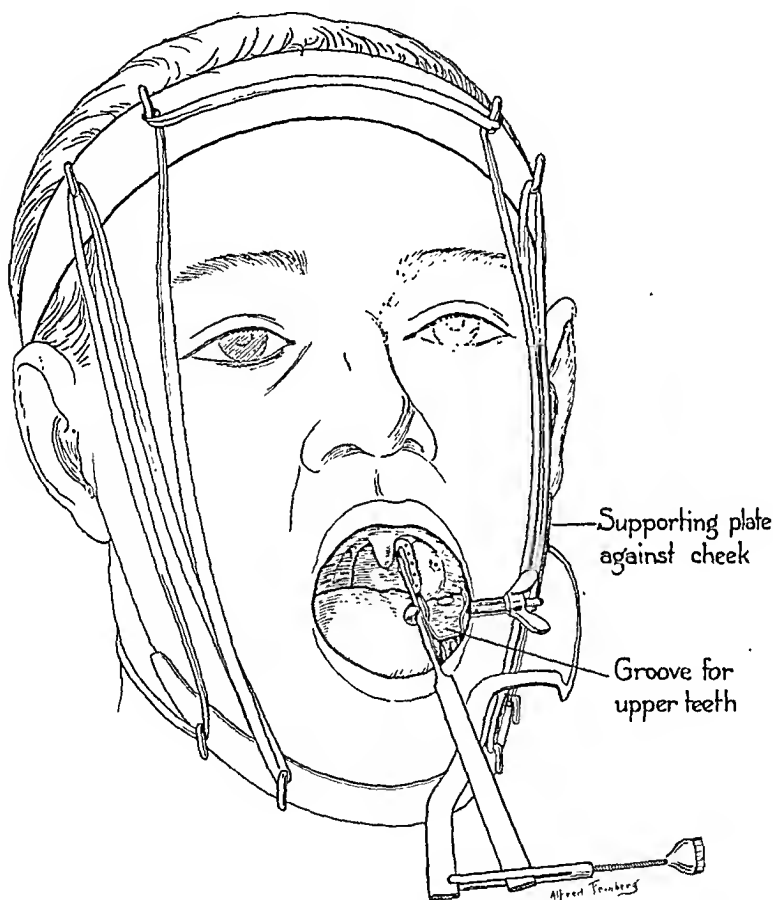


Fig. 15.—The Berven tonsil applicator for the surface irradiation of the tonsillar region. For clarity, the diagram shows the moulage against the tonsil to be small, whereas in practice it covers the entire tonsil.

cheek. It is sometimes necessary to apply this applicator on successive days if the dose is so high that more than ten hours is required for the treatments.

*Malignant Tumor of the Antrum or the Superior Maxilla.*—Surgical resection is the sole method of treatment for the rare osteosarcoma and chondrosarcoma of the antrum and the superior maxilla. The frequent epidermoid carcinoma of the antrum is treated by a combination of

surgical intervention and irradiation. It is difficult to sterilize the cancer by radium alone because of the danger of radionecrosis, prolonged supuration and cachexia; hence the radium therapy is always preceded by surgical drainage and *épluchage*. The x-rays are employed as a routine as a preoperative and supplementary measure. The antral epithelioma grows rapidly, becomes secondarily infected and early invades the nasal fossae, the alveolus, the inferior border of the orbit and the malar bone. There are two stages in the development of carcinoma of the antrum.

In the first stage the carcinoma may invade the alveolar process and even the nasal fossae, especially the anterior ethmoid cells and the

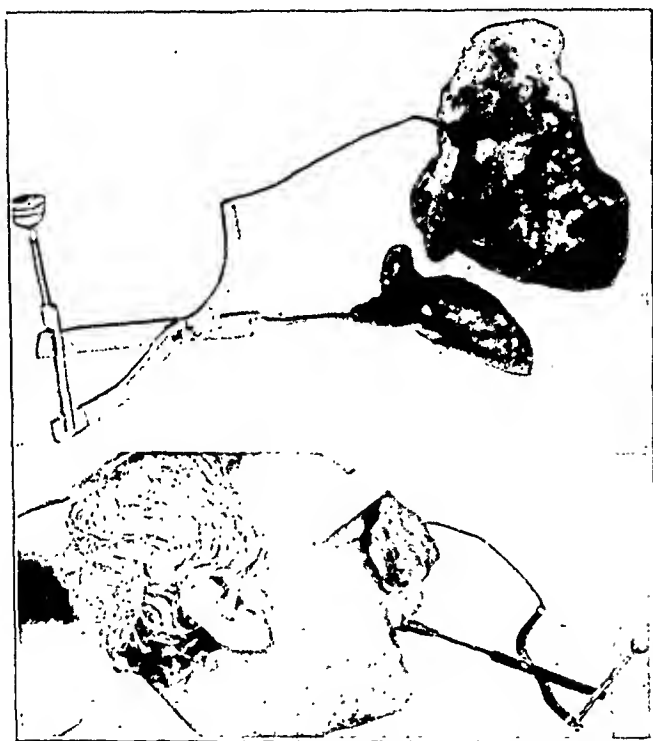


Fig. 16.—The Berven radium applicator used in the treatment of cancer of the palate. The best way for maintaining contact application of a radium moulage in the mouth of an edentulous patient.

internal part of the floor of the orbit. The skin, lymph glands, orbit and palate are not invaded. An incision is made along the nasolabial fold and through the middle of the upper lip to afford sufficient reflexion of the flap to permit exploration of the sinuses and correct placement of the radium tubes or needles. As much of the involved bone is removed as possible, followed by curettage of the cavity. The radium treatment begins immediately after the operation. Radium needles with a platinum filter of 0.5 mm. and a radium content of 3.33 mg. each are packed in

gauze and distributed equidistantly throughout the wound. The average dose is from 20 to 25 millicuries destroyed (from 2,660 to 3,325 milligram hours) given by from ten to fifteen radium needles for from fifty to seventy-five hours. Radium therapy is superior to roentgen therapy in this location because its action is limited, it does not injure the eye, the irradiation is more selective and the skin and hair are less affected. Supplementary roentgen treatment is sometimes given after the radium treatments.<sup>15</sup>

In a more advanced stage, the skin and lymph nodes may be involved as well as the orbit, the temporal fossa, the palate, the nose and even the intracranial cavity. The results from radium therapy and surgical measures are not so good as in the preceding class. Ligation of the external carotid artery is done, followed by a radical resection of bone, including the malar bone and the inferior orbital border, and, if necessary, exenteration of the orbit. The skin should be widely excised if it has been invaded. The prosthesis is not made until cicatrization is complete, which requires from two to six months. Local recurrence is readily detectable, and if it occurs it is accessible because of the character of the operation; such a lesion is treated by radium therapy.

*Carcinoma of the Larynx.*—Laryngeal carcinoma may be classified according to the site of its origin, e. g., intrinsic on the vocal cords, extrinsic above the vocal cords and subglottic below the vocal cords. Such cancer may also be subdivided into two types by the character of the differentiation. One type, chiefly intrinsic in location, is an epidermoid carcinoma, papillary or infiltrating, which differentiates into sterile squamous sheets and pearls. True prickly cells are found in this tumor. The nuclei frequently disappear entirely. The tumor cells are highly eosinophilic. This epidermoid carcinoma, referred to as the cutaneous type, is relatively radioresistant as compared with the mucous membrane type, which is chiefly extrinsic in origin. In the mucous membrane type, the differentiation is less complete, the pyknotic nuclei are retained in the pearls, prickly cells are lacking and the tumor does not take an intensely pink stain with eosin. The mucous membrane type is more frequently observed on the ventricular fold and is very radiosensitive as a rule.<sup>15</sup> The localization of a vascular, papillary carcinoma on the ventricular fold seems to indicate great radiosensitivity. The classification and histologic grading of the tumor are done by means of biopsy specimens obtained by direct laryngoscopy.

Extrinsic carcinoma of the larynx is treated by external irradiation alone. If the epidermoid carcinoma is of the mucous membrane type

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15. Pack, G. T.: The Management of Malignancies of the Antrum, Superior Maxilla, Pharynx and Larynx at the Radium Institute of the University of Paris, *Ann. Otol., Rhin. & Laryng.* 37:967, 1928.

of differentiation, regardless of whether it is intrinsic or extrinsic in location, irradiation only is used. The factors used in the roentgen treatment of such a tumor are: 200 kilovolts, 30 milliamperes, a filter of 0.5 mm. of copper and 2.5 mm. of aluminum and a target-skin distance of 60 cm. Although Regaud used four portals, two anterior and two posterior, I have employed only the two anterolateral portals directed to cross-fire at the larynx. A total dose of from 3,000 to 4,200 roentgens is given to each side by the fractionated method with only from 250 to 300 roentgens daily, alternating to each side of the neck. With the foregoing factors, 475 roentgens constitutes a threshold erythema dose for the skin, and 850 roentgens given at one exposure will produce a sharp erythema. Three weeks or so is needed in which to deliver this dose. Certain accidents, such as edema of the larynx, necrosis of the cartilage and intense reaction of the skin or mucous membranes, may occur. They may be prevented in some cases by a preliminary tracheotomy (if necessary), the removal of foci of infection or the removal of cartilage invaded by the carcinoma. The invasion of cartilage may be detected by lateral roentgenograms of the larynx, which are made as a routine. It is extremely difficult to sterilize cancer cells embedded or growing in a cartilaginous base.

Instead of relying exclusively on external irradiation, supplementary intracavitary irradiation may be employed in some cases of intrinsic carcinoma of the larynx. With this combination there is less need for such intensive roentgen treatment. The applicator is modeled after the one designed by Dr. Henry Schmitz, of the Mercy Hospital Institute of Radiation Therapy in Chicago, and later modified by Dr. Walter L. Mattick, of the State Institute for the Study of Malignant Diseases.<sup>16</sup> This applicator is a large intubation tube of the O'Dwyer model, except that the central air space is surrounded by a cylindric chamber containing twelve concentric grooved holes each 1 mm. in diameter. These grooves extend lengthwise of the tube, and each is capable of holding two of the platinum-filtered radium cells placed end to end, so that the source of radiation is well distributed within the larynx. The inner cylinder containing the cells may be made of aluminum, brass or gold, depending on the degree of filtration desired. The lower end of the tube is hard rubber rather than metal in order to lessen the weight of the applicator. The cap which screws over the top of the radium-bearing cylinder is flanged so that it will rest on the glottis and contains a small eye for a thread, which is attached to facilitate its removal. The assembled radium intubation tube is introduced into the larynx, by the usual O'Dwyer technic, where it may be seen in position by inspection with

16. Mattick, W. L.: Some Additions to Our Radiologic Armamentarium in the Treatment of Esophageal and Laryngeal Cancer, New York State J. Med. **33**:863-865 (July 15) 1933.



a laryngeal mirror. The tube is left in place for four hours daily, at which time the patient is mildly narcotized. The quantity of radium employed, i. e., the intensity, varies from 32 mg. (twenty-four cells of 1.33 mg. each) to 80 mg. (twenty-four cells of 3.33 mg. each). The dose varies between 750 and 1,200 milligram hours, depending on the character of the lesion being treated, the degree of filtration used and the quantity of x-radiation employed. Treatments are given daily until the total dose is delivered. This intralaryngeal irradiation never precedes the roentgen treatments. Tracheotomy is not necessarily needed but usually is done until the radium treatments have been completed (fig. 17).

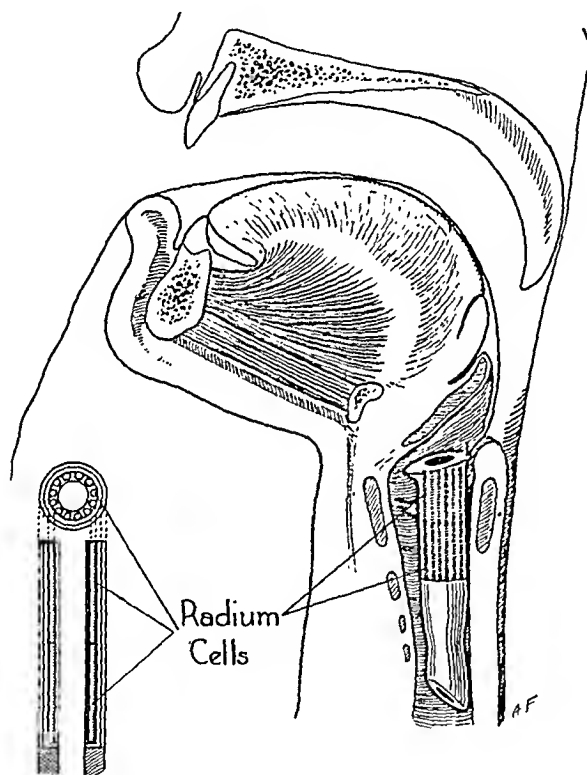


Fig. 17.—Mattick modification of the Schmitz intralaryngeal radium applicator. The O'Dwyer intubation tube is designed to contain two tiers of radium cells arranged concentrically around the lumen. The inner cylinder containing the cells may be made of aluminum, brass or gold, depending on the degree of filtration desired.

An early squamous cell carcinoma on the anterior half of one vocal cord is sometimes dealt with by operative removal. Hemilaryngectomy by the technic of St. Clair Thomson is preferred to such extremes as simple chordectomy or total laryngectomy. The indications for laryngofissure and interstitial radium therapy are becoming less important with the recent marked improvements in external irradiation, although occasionally this procedure has been carried out.

*Tumor of the Parotid Gland.*—Mixed tumor of the parotid gland is excised surgically. This may be accomplished in practically every case, whether the growth is primary or recurrent, without injury to the facial nerve. The operation is greatly facilitated by preliminary sialography with iodized poppy-seed oil 40 per cent to show the relation of the tumor to the uninvolved parenchyma of the gland. Postoperative external irradiation with radium or roentgen rays induces considerable fibrosis in the gland and is thought to prevent or retard recurrences.

Carcinoma of the parotid gland is treated by a combination of external and interstitial irradiation. High voltage (200 kilovolts) x-rays are applied through a cone directly to the gland and with such a small field that the fractionated doses of from 200 to 250 roentgens may be continued daily until a total dose of from 4,000 to 5,600 roentgens has been delivered. Whenever supplementary interstitial irradiation is deemed necessary, the small single cell radium needles are inserted in gridiron fashion to surround the tumor.

*Metastatic Carcinoma in the Cervical Lymph Nodes.*—In general, it may be stated that metastatic carcinoma in the cervical lymph nodes is of a higher degree of radioresistance than the original primary intra-oral tumor, although there are occasional exceptions to this rule.<sup>12</sup> The radiosensitivity of such a metastatic carcinoma, however, does depend on the character of the primary tumor; e. g., the transitional cell carcinoma and the lympho-epithelioma frequently metastasize to groups of nodes rather than in a single focus, and such metastases are without exception very responsive to irradiation. Carcinoma in the nodes secondary to squamous cell carcinoma of the lip, tongue or cheek can never be controlled by external irradiation alone, either by single intensive treatments or by the application of the Coutard principle of fractionated doses of high voltage x-rays or gamma rays. Carcinoma in such a node forms keratin, is prone to spontaneous degenerative changes, such as liquefaction, and may exhibit desmoplastic fibrotic changes after external irradiation without sterilization of the node. On this account such nodes are treated by the combination of external and interstitial irradiation; the small Treves single cell needles are inserted through the lymph node to deliver a tissue dose in millicuries destroyed based on the size of the node and utilizing the table of dosage requirements previously mentioned. The node is exposed by a small incision through the skin and subcutaneous tissues made with the patient under local anesthesia; the needles are inserted with attached threads to permit removal after delivery of a specified dose. In the case of larger fixed carcinomatous masses in the neck in which the capsules of the nodes have been perforated, transcuteaneous puncture is sometimes indicated and larger needles, some containing two platinum cells in tandem, are inserted if

the node is of sufficient size. It is seldom that this supplementary interstitial radium therapy is needed for metastatic carcinoma of the transitional cell or lympho-epithelioma type.

The great problems in the management of these nodes is the consideration of indications and contraindications for a radical or partial cervical dissection and of when to employ radiation therapy in lieu of surgical excision. The best answer to this problem has been furnished by Dr. James J. Duffy:

Indications	Contraindications
1. Metastases limited to one node or group of nodes	1. No apparent metastatic involvement of nodes
2. No perforation of capsule of lymph nodes	2. Perforation of capsule by carcinoma
3. Primary lesion controlled or controllable	3. Primary lesion uncontrolled or uncontrollable
4. Opposite side of neck free from disease	4. Crossed metastasis or bilateral metastasis present
5. Primary lesion limited to one side of oral cavity	5. Extension of primary lesion to or beyond the midline
6. Primary lesion composed of highly differentiated cells	6. Primary lesion composed of undifferentiated cells
7. No distant metastases	7. Distant metastases present
8. Patient in good general health	8. Patient in poor general health or aged
All these indications must be present for dissection.	Any one of these contraindications preclude radical dissection.

A study of this tabulation reveals the interesting fact that the operability of the cervical nodes is determined by the grade of malignancy of the primary lesion as well as by the extent of the metastases. The data are self-explanatory and will not require further comment here.

Prophylactic cervical dissection for intra-oral cancer is never employed. This radical operation is attended by an appreciable mortality and considerable morbidity. Not more than from 10 to 12 per cent of the operations so done will reveal any metastatic foci in the nodes removed; delay in operation in these particular cases would not necessarily be fatal, as many cases are salvaged when recognized metastases are present in the cervical nodes. In an analysis of nine hundred and eighty-three patients with intra-oral cancer admitted to the Memorial Hospital without clinical evidence of metastasis in the cervical nodes, Dr. Duffy found that at the end of three years metastases had not developed in 80 per cent of these patients, which would indicate that in this group 80 per cent of the prophylactic cervical dissections would be unnecessary. It must be realized, however, that all patients with intra-oral carcinoma who do not have evident metastatic involvement in cervical lymph nodes should be examined at frequent intervals so that if such metastases do become apparent they may be treated without harmful delay.

If there are palpable diseased nodes in the neck they are not molested until after the reaction of the intra-oral carcinoma to the radium has sufficiently subsided (a period of about three weeks). Then, if the indications fully warrant it, a unilateral complete block dissection of all the cervical lymphoid tissue is performed. Every lymph node is examined histologically; if carcinoma is found, as is usually the case for the indicated dissection, the neck is irradiated postoperatively and prophylactically by high voltage x-rays or radium therapy at a distance. If no microscopic evidence of carcinoma is discovered in the excised tissues, i. e., if it is inflammatory only, then the neck is not irradiated but carefully watched.

*Cancer of the Esophagus.*—Preliminary esophagoscopy serves two purposes in cases of esophageal cancer: First, it enables one to obtain a biopsy specimen for histologic grading and determination of the radio-sensitivity of the carcinoma, and second, it enables one to measure the distance of the lesion from the incisor teeth. Fluoroscopy also informs one of the extent of the carcinoma and its topographic location, which is recorded at this time by indelible markings on the body anteriorly and posteriorly. Accurate localization of the lesion is necessary in order to insure proper direction of the x-ray beams and the correct placement of radium.

A Janeway gastrostomy, constructed of a tubed pedicled flap from the anterior wall of the stomach and lined by mucosa, is the first step in the treatment. It avoids irritation and lessens infection of the stenosing carcinoma, permits a high caloric diet and proper intake of fluids during irradiation and later enables the retrograde insertion of radium.

With the location and extent of the carcinoma marked anteriorly and posteriorly, four small paramedial ports are selected through which the x-rays are directed to cross-fire at the lesion. These skin portals are the right and left anterior paramedial portals and the right and left posterior paramedial portals. The high voltage x-rays (200 kilovolts peak voltage) are given through a filter of from 0.5 to 1 mm. of copper at 70 cm. target-skin distance. Three hundred roentgens are given to each of the right skin portals, alternating daily with the left skin portals, until from 2,000 to 2,400 roentgens is delivered to each portal. These treatments are completed in from two and a half to three weeks.

Roentgen irradiation is followed in some cases by intracavitary radium therapy. A heavy waxed braided silk thread with a BB shot attached at its end is swallowed by the patient. This string is anchored to the cheek or ear with adhesive tape. A bronchoscope, cystoscope or child's esophagoscope is introduced through the gastrostomy orifice, and the string is grasped and withdrawn on the abdomen. A rubber-enclosed string of radium capsules, from two to four in number, depending on the linear dimension of the cancer, is tied to the string and drawn

into the stomach and then into its proper position in the esophagus. The correct placement of this tandem (the capsules are arranged end to end) is verified by fluoroscopy. Each capsule contains five cells of 3.33 mg. each, or a total of 16.65 mg. of radium. The filter is at least 1 mm. of platinum, as only the very short gamma rays are employed. The dose varies from 1,000 to 1,500 milligram hours (from 8 to 12 millicuries destroyed). Interstitial irradiation of esophageal cancer is contraindicated because of the difficulties and dangers in the correct placement of the seeds and needles, the dose is too caustic and intense, and perforation of the organ with formation of a mediastinal abscess is a possibility in view of the fact that the esophagus does not have a serosal coat.

*Cancer of the Stomach.*—The treatment of gastric cancer is largely surgical. If the lesion is situated in the distal half of the stomach and is classified as operable, subtotal gastrectomy offers the best opportunity for palliation or even permanent arrest of the disease. The various modifications of the Billroth I operation share in its disadvantages, such as more frequent local recurrence and obstruction. The Billroth II resection and anastomosis are frequently used with the aid of the de Petz sewing clamp. The posterior Polya and anterior Balfour anastomoses are also highly satisfactory. Partial gastrectomy is done occasionally in the presence of distant inoperable metastases, as it is considered a better palliative measure than gastro-enterostomy alone. Resection is occasionally done in two stages in elderly patients with complete pyloric obstruction, when they are considered poor operative risks; the first step is a simple gastro-enterostomy. The second step, or resection, is done in from ten to twenty days after anastomosis has been successfully accomplished. Total gastrectomy should be done if the carcinoma is confined to the stomach and extends into the cardia or fundus, provided the abdominal esophagus is free, mobile and of sufficient length to support an anastomosis. In this operation the esophagus may be sutured either to the duodenal stump or to a jejunal loop. Gastro-enterostomy in itself is not very successful as a palliative measure for gastric cancer; the patient lives to suffer longer. When gastro-enterostomy is supplemented by a simple closure of the involved distal cancer-bearing segment of the stomach, the patient experiences marked relief. Although the cancer is not removed, the proximal part of the stomach is clean, the anorexia disappears, the ulceration and infection of the cancer diminish, the contamination of food is avoided and the danger of later obstruction of the gastro-enterostomy stoma is prevented.

The treatment for the gastric cancer which is classified as inoperable because of fixity, metastases or location (cardia) is palliative radiation therapy. It is well known that carcinoma of the stomach is generally radioresistant. Moreover, the inaccessibility of cancer in this location,

its proximity to the adjacent labile viscera and the necessity of a laparotomy for the insertion of radium have presented other handicaps to successful radiation therapy. Some of these handicaps have been overcome by new technical methods, and some of the cancers, especially those near the cardia, have exhibited various degrees of radiosensitivity. The efforts at radiation therapy have been directed mostly to cancer of the gastric cardia and of the fundus. Gastroscopy and biopsy precede the treatment.

The location and extent of the carcinoma as determined by fluoroscopy are marked on the body surface anteriorly, posteriorly and laterally (left). High voltage x-rays (200 kilovolts) with a filter of 0.5 mm. of copper and at 70 cm. target-skin distance are directed to cross-fire through these portals. A dose of from 250 to 300 roentgens daily is given until each skin port receives a total of from 2,400 to 3,000 roentgens.

External irradiation is occasionally supplemented by interstitial irradiation in the treatment of carcinoma of the cardia. Gold radon seeds are preferable to needles for this technic; however, the latter may be employed if due caution is observed. The cardia and fundus are exposed by a Baudet-Novarro incision running below and parallel to the left costal margin. A costochondral rib flap is either turned up and later replaced and sutured or excised, thereby permitting a more direct approach to the cardia. The small Treves needles containing a single radium cell are inserted obliquely into the cancer so as not to perforate the wall of the stomach. Attached threads for withdrawal are pulled through a cigaret drain, which is removed at the same time as the needles, usually from thirty-six to forty-eight hours later. At the same time a Janeway gastrostomy is usually done. If the carcinoma is bulky and mostly intragastric, other radium needles may be inserted directly into it through an endoscope (bronchoscope, cystoscope or child's esophagoscope) passed through the gastrostomy opening. As much as 40 millicuries destroyed (5,320 millicurie hours) has been delivered interstitially into a gastric cancer. This treatment is still in the experimental stage, although some palliative results have been obtained.

*Carcinoma of the Colon.*—The usual operation for carcinoma of the cecum, ascending colon or hepatic flexure is done in two stages. First an ileocolostomy is performed, the transverse colon being used, and later resection of the cecum and the ascending colon is carried out. When a carcinoma of the sigmoid flexure, descending colon or splenic flexure is complicated by acute obstruction, a preliminary cecostomy or proximal colostomy is performed, and the resection is done at a later date; the cecostomy serves as a safety valve after resection, and if it is properly done (Witzel technic) the opening will close spon-

taneously. In cases in which there is no obstruction, the Rankin operation of obstructive resection is done, the tumor being removed and the two blind "gun-barrels" being closed for from forty-eight to seventy-two hours. Radiation therapy is seldom indicated for cancer of the colon. Some carcinomas of the cecum are radiosensitive, but irradiation here is reserved for the inoperable or recurrent cancer.

*Carcinoma of the Rectum.*—Resection of the rectum by any of the approved surgical methods offers the best opportunity for cure of carcinoma of the rectum. However, there are two classes of patients for whom other methods of treatment must be employed, namely, those with inoperable cancers of the rectum and those who refuse operative intervention. Irradiation is not necessarily confined to these groups, as it is often a valuable supplement to surgical treatment as a pre-operative or postoperative measure. A rectal cancer histologically classified as of grade 3 or 4, on the basis of the differentiation receives a pelvic cycle of high voltage x-rays directed through four skin portals, two anterior and two posterior, to cross-fire at the rectum; fractionated doses of 300 roentgens are given daily to alternate portals until 2,000 or 2,400 roentgens is given to each area. The effect of these treatments is seen in the great diminution in the size of the tumor, its increased mobility, the subsidence in the degree of infection and the general improvement of the patient. Resection of the rectum is then carried out from four to six weeks later.

A carcinoma situated in the rectal ampulla and classified as operable may be treated in the following sequence: preliminary treatment with high voltage x-rays, then colostomy followed by interstitial irradiation with radium element needles, and finally perineal resection.<sup>17</sup> Interstitial irradiation prior to surgical resection is seldom used except for the infiltrating carcinoma which is classified histologically as grade 2. External irradiation is never used prophylactically for postoperative treatment; it is employed only when the surgeon considers the resection incomplete or a local recurrence has actually developed.

The technic for the irradiation of the rectal cancer will be summarized briefly. After completion of the roentgen treatments, as previously described, the main reliance must be placed on interstitial irradiation. Intracavitary irradiation with a tandem of radium capsules or the surface application of radium within the rectum is seldom indicated except when used to enlarge the lumen through a stenosing carcinoma.

A most necessary adjunct to successful radium therapy is colostomy, performed with a short distal segment in order to facilitate retrograde

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17. Binkley, G. E.: Colostomy, Radiation Therapy and Perineal Resection for Cancer of the Rectum, J. A. M. A. 99:1592-1596 (Nov. 5) 1932.

sigmoidoscopy. Other advantages afforded by the colostomy are: the short circuiting of the fecal current and avoidance of contamination of the cancer during treatment, subsidence of infection in the cancer and facility in irrigation of the cancer bearing segment in preparation for the introduction of radium.

Sheath needles containing one or two of the platinum radium cells are inserted into and through the base of the tumor through the anus, either by guidance along a palpating finger when the cancer is situated low or through a proctoscope under direct vision. The needles are placed usually in the longitudinal axis of the rectum and are distributed circumferentially. Additional needles may be inserted through small

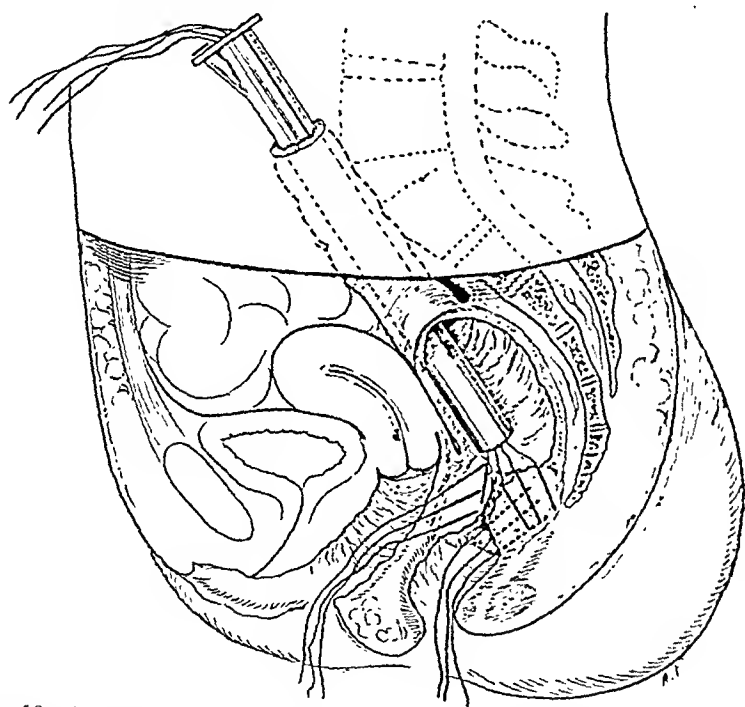


Fig. 18.—Method of interstitial radium therapy for rectal cancer in the female. The single cell radium needle is inserted through the anal orifice and the posterior vaginal wall, and a sigmoidoscope is passed in retrograde direction through the short lower limb produced by a loop colostomy.

puncture wounds in the perineal and postanal regions when the carcinoma infiltrates anteriorly or posteriorly, respectively. The superior pole of the cancer is best approached through a sigmoidoscope passed downward through the inferior stoma of the double-barreled colostomy opening. Through this instrument additional radium needles may be inserted from above (fig. 18).

In females, cancer situated in the anterior wall of the lower part of the rectum may also be treated by the introduction of these needles



into the tumor through the posterior vaginal wall. This placement can be done accurately if the index finger of the left hand is inserted in the rectum to guide the direction of the needles. Overdosage in this location may result in a rectovaginal fistula. A longitudinal incision may be made posterior to the anus and extending above the coccyx, which may be removed to afford better exposure of the ischiorectal fossa. Through this opening additional radium needles are placed around the cancerous segment of the rectum in the manner of a barrage. This procedure has been employed by Sir Charles Gordon Watson.

Double waxed silk threads are attached to the needles for their removal, which is usually done on the third to the fifth day. The total dose depends on the size and extent of the tumor and its local characteristics. The dose is seldom greater than 50 millicuries destroyed. In one instance the radium needles were introduced through a postero-superior proctotomy; a vertical incision was made posterior to the anus and above the sphincter, which was not harmed. The coccyx and terminal two sacral vertebrae were removed, exposing the rectum. The rectum was then incised longitudinally, and radium was inserted into the cancer under direct vision. This procedure is feasible only when the tumor is situated high in the rectum.

*Tumor of the Kidney or Adrenal Gland.*—Any operable renal or adrenal neoplasm is treated by nephrectomy followed by prophylactic high voltage roentgen treatment. Inoperable, recurrent and metastatic hypernephroma, renal papillary adenocarcinoma and epithelioma of the renal pelvis are also treated by fractionated doses of high voltage x-rays but without much success, as the few tumors of this type treated have proved to be radioresistant. The embryonal adenomyosarcoma of the kidney (Wilm's tumor) occurring in children has a high degree of radiosensitivity and usually regresses completely after heavy roentgen treatment; this intensive preoperative irradiation is followed by nephrectomy after the regression has reached its limit; otherwise recurrence is the rule (Dean and Pack<sup>18</sup>).

*Benign or Malignant Tumor of the Urinary Bladder.*—Whenever one or two benign papillomas of the bladder can be visualized through the cystoscope, it may be possible to remove them by an endotherm snare, which procedure is always followed by the insertion of gold radon seeds into the base of the tumor, after the method originated by Barringer.<sup>19</sup> Papillary carcinoma also may be treated through the urethra

18. Dean, A. L., Jr., and Pack, G. T.: Embryonal Adenocarcinoma of the Kidney, *J. A. M. A.* **98**:10-17 (Jan. 2) 1932.

19. Barringer, B. S.: The Past and Present in Genito-Urinary Carcinoma, *Am. J. Surg.* **23**:438-441, 1934.

by this method, if the base of the tumor is not larger than 1.5 cm. in diameter. The dosage for these treatments has been determined by Dean and Quimby<sup>20</sup>; gold radon seeds of 2 millicuries each are buried to the depth of 1 cm. and placed 1 cm. apart.

The papillary carcinoma, regardless of size, and the flat infiltrating carcinoma are exposed by suprapubic cystotomy for the more accurate placement of radium foci. Dean and Quimby have shown by experiments that a larger number of relatively weak sources of radiation are preferable to fewer strong radium foci. Hollow sheath needles are accurately inserted into the base of the tumor through the suprapubic wound; attached threads for the removal of these needles are drawn through the suprapubic wound and anchored to the abdominal wall. The threads are impregnated with yellow wax so that they will not become weak and rotten while constantly immersed in urine. These single cell needles are placed at intervals of 1 cm. The following scheme of dosage is employed. Needles containing 3.33 mg. cells give a dose of 2 millicuries destroyed (266 milligram hours) per square centimeter of tumor base if left in situ for eighty hours. Sixty hours of interstitial radiation with needles of this strength will deliver a dose of 1.5 millicuries destroyed (200 milligram hours) per square centimeter of tumor treated. If the needles contain the cells of less radium content—the 1.33 mg. cells—the duration of treatment must be one hundred hours in order to give a dose of 1 millicurie destroyed per square centimeter; this dose is not always cancerocidal.

High voltage roentgen treatment is chiefly employed as a palliative measure for inoperable and recurrent carcinoma of the bladder. It is more successful for papillary carcinoma and may be used postoperatively as a supplement to interstitial irradiation. At a distance of 100 cm. and with a low daily dose of only 100 roentgens, Ferguson in a series of cases has successfully controlled papillomatosis of the bladder, ureter and kidney.

*Carcinoma of the Prostate.*—Prostatic cancer is first treated by a pelvic cycle of high voltage x-rays. Cancer of the prostate in the advanced stage with demonstrable metastases is treated solely by fractionated doses of x-rays, from 250 to 300 roentgens being given daily to one of the four pelvic portals and alternated daily until 2,000 or 2,400 roentgens are delivered. The target-skin distance is 70 cm., the filter 0.5 mm. of copper and the milliamperage 20, and the beams of radiation are directed to cross-fire at the prostate. The entire cycle is seldom completed in less than one month. When roentgen therapy is to be followed by interstitial irradiation, only four exposures of 750

20. Dean, A. L., Jr., and Quimby, E. H.: Radiation Therapy of Carcinoma of the Bladder, Surg., Gynec. & Obst. 53:89-96, 1931.

roentgens each are given to the pelvic portals. As Barringer has found that the average carcinoma of the prostate requires 10 skin erythema units as a tissue dose delivered to all parts of the tumor in order to effect its complete destruction, roentgen therapy must be supplemented by interstitial irradiation.<sup>19</sup>

Interstitial irradiation of the prostate is accomplished through two ports of entry. With the patient under sacral anesthesia, a stab wound is made in the perineum, and through this opening from eight to ten radium bearing needles (contents either 1.33 or 3.33 mg.) are introduced into the prostate. These needles are affixed in the hollow-cupped ends of long-handled rods, which facilitate their introduction through the perineum and are easily dislodged when in the prostate, leaving the needles in place with strings attached for withdrawal. They are directed and accurately placed with two fingers of the other hand in the rectum. Other single cell needles are inserted through the incision made for a suprapubic cystotomy. The base of the bladder is exposed by the assistant. The operator stands on the patient's left and with two fingers of his left hand in the rectum inserts the needles through the suprapubic wound into the prostate with the right hand. The dose depends on the size of the prostate; it seldom totals more than 50 millicuries destroyed (6,650 milligram hours) and is computed at from 1 to 2 millicuries destroyed per cubic centimeter of tissue irradiated.

*Epithelioma of the Penis.*—When a penile cancer is early, superficial and situated on the prepuce, circumcision is done, followed by topical radium therapy. Radium therapy by surface application is also suitable for early cancer of the glans penis. A square, rectangular or round plaque (as previously described) is selected, according to the surface area to be irradiated. The radium-skin distance, filter, intensity and dosage are the same as for epithelioma of the skin. Or an individual wax moulage may be molded for each individual patient and platinum cells of 3.33 mg. content embedded at a depth of from 0.25 to 0.5 cm. to give a dose of from 0.8 to 3 millicuries destroyed (from 100 to 400 milligram hours) per square centimeter of skin area. The glans and preputial skin are quite sensitive to irradiation and will not tolerate interstitial irradiation without danger of radionecrosis. Partial or radical amputation may be necessary for more advanced epithelioma, followed by prophylactic external irradiation of both groins. If the inguinal lymph nodes are involved by metastatic carcinoma, bilateral inguinal dissection is done as a second stage operation. The inguinal dissection should be done prior to external radium therapy or high voltage roentgen therapy; otherwise tissue changes due to radiation delay the healing of the inguinal wounds. In Barringer's wide experience, involvement of the inguinal lymph nodes by carcinoma occurs in

only 40 per cent of the cases of penile cancer, on which account routine prophylactic dissection of the groin has not been adopted. An alternative to dissection of the groin is exposure of the carcinomatous nodes and implantation of one cell radium needles.<sup>10</sup>

*Teratoma of the Testis.*—The malignant testicular neoplasm is treated by a combination of external irradiation followed by orchidec-tomy. The initial response of the tumor, as judged by the rapidity and extent of reduction in size, indicates to some degree the histologic type of tumor. Although it is possible to sterilize the embryonal carcinoma and seminoma by external irradiation, one may never rely on that method

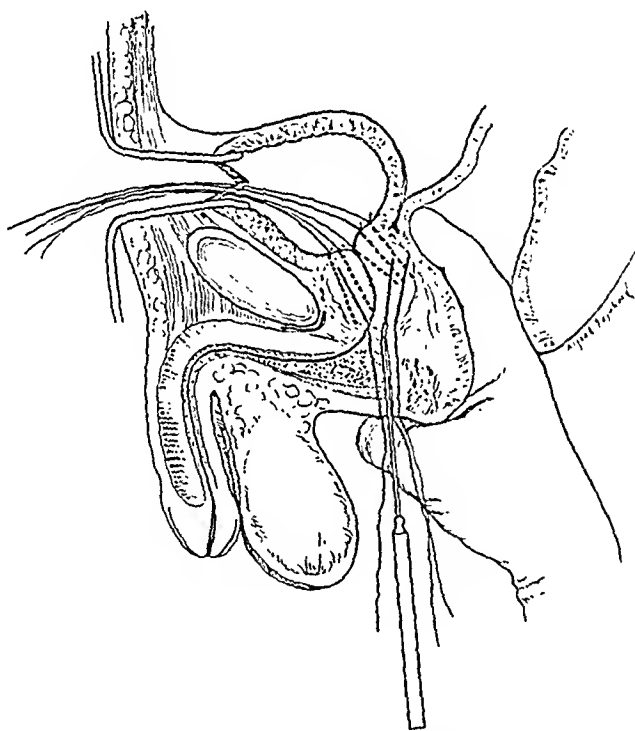


Fig. 19.—Method of interstitial radium therapy for prostatic cancer. The single cell or two cell radium sheath needles are introduced into the prostate gland through a suprapubic cystotomy and the perineum. The insertion and guidance of the direction of the needles inserted through the perineum are aided greatly by the insertion of a forefinger in the rectum.

for the control of the tumor. The advantages of postradiation orchidec-tomy are: first, it prevents overirradiation to the opposite testicle; second, it removes all the local neoplasm, including the radioresistant portions of the adult teratomas, and, finally, it enables the pathologist to classify the tumor, which is of great aid in judging the few methods of treatment. The abdominal metastases are treated by external irradiation only, roentgen rays of 200 kilovolts, a 0.5 to 1 mm. copper filter

and a target-skin distance of from 70 to 100 mm. being used for a large skin port both anteriorly and posteriorly and fractionated doses of 300 roentgens being given daily to alternating areas until a total of from 2,000 to 3,000 roentgens is given.

The most important contribution to the successful management of this tumor is the estimation of a follicle-stimulating principle in the urine as perfected by Ferguson. The quantitative estimation of this principle in the urine may not only indicate the embryonal character, the degree of malignancy and consequently the response to radiation of the primary tumor, but may serve to detect abdominal metastases or recurrences long before these lesions are palpable.

*Malignant Tumors of the Vulva.*—The treatment of vulvar epithelioma is essentially a surgical problem. Radiation therapy is followed by immediate edema, swelling and marked inflammatory reaction accompanied by extreme pain and the danger of late radionecrosis. The moist vulvar skin does not tolerate external irradiation well, and the tissues are too delicate and sensitive to permit of interstitial irradiation. Furthermore, the vulvar epithelioma is usually a radioresistant cancer with a histologic grading of 1 or 2. Vulvectomy is usually the best procedure, followed by prophylactic external irradiation of both groins. If the inguinal lymph nodes are involved by metastatic carcinoma, bilateral inguinal dissection is done as a second stage operation. The inguinal dissection should be done prior to heavy external radium therapy or high voltage roentgen therapy, otherwise the tissue changes due to radiation delay the healing of the inguinal wounds. In a few cases, I have implanted the small one cell radium needles in the exposed inguinal or femoral nodes, but I have not been impressed by the results of this method of treatment. I am more and more impressed with the ultimate necessity of a second stage bilateral inguinal dissection even though no metastases are evident.

*Carcinoma of the Cervix.*—The majority of carcinomas of the cervix (97 per cent) are of the epidermoid type, histologically graded as squamous, plexiform and anaplastic; the other 3 per cent are adenocarcinomas, though some of these may have originated in the corpus. The selection of the radiotherapeutic procedure depends more on the stage or extent than on the histologic structure of the tumor. In this consideration the classification adopted is the one formulated by the Radiological Subdivision of the Cancer Commission of the League of Nations.

Stage 1: The carcinoma is limited entirely to the cervix. The uterus is movable, and no paracervical induration is detectable.

Stage 2: The carcinoma has extended to involve part of the vaginal fornices slightly, with or without some induration of the paracervical tissues. The uterus has some degree of mobility, and the stage is one of borderline operability.

Stage 3: The uterus is partly or completely fixed, with induration of the parametrium on one or on both sides, or there is involvement of a considerable portion of the vagina, though the uterus is movable.

Stage 4: The cancer has invaded adjacent viscera, involves most of the vagina and has metastasized beyond control. It is incurable.

The radical panhysterectomy (Wertheim) can be done only for cervical cancer in stage 1, but even in this early stage the results of treatment are not better than when radiation therapy is employed. There are few gynecological surgeons trained to do this formidable operation, of which the morbidity and mortality are considerable; on the other hand, radiation therapy is so well planned, standardized, easy to execute and free from danger that it permits of more general usage. Surgical treatment is absolutely indicated in those cases of cancer of the cervix in which radium therapy is inefficient or dangerous. It is considered to be inefficient when the cancer is known to be radio-resistant, as when an operable cancer has been treated by radium therapy and has proved radioresistant, so that more irradiation might cause radionecrosis. In such a case hysterectomy is the last possible method of treatment. Radium therapy is often insufficient for a cancer which is very feebly radiosensitive, such as an adenocarcinoma. The utero-vaginal method of applying radium is inefficient when a malformation of the uterus (atresia, irreducible flexion) or of the vagina (congenital or cicatricial stenosis) will not permit the typical and correct technic. If the cancer is operable, it is best to practice hysterectomy and reserve radiation therapy (x-rays and external foci of radium) as a resource against recurrence. Radiation therapy is dangerous when the cancer is complicated by adnexal inflammation. One may attempt to suppress the inflammatory process and, if sufficiently successful, may later attempt surgical removal followed by external irradiation.<sup>21</sup> Before either radium or roentgen therapy is given, the possibility of latent or chronic pelvic inflammatory disease should be ruled out. Irradiation under such circumstances is fraught with many dangerous complications, such as salpingitis, pelvic phlegmon, peritonitis and septicemia. These accidents seldom occur if the vaginal flora is free from streptococci.

A cervical cancer in stage 4 is not suitable for any form of treatment. All cervical lesions in stages 1, 2 and 3 are treated by irradiation.

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21. Pack, G. T.: The Management of Uterine Malignancies at the Radium Institute of the University of Paris, South. M. J. 21:505-515, 1928.

tion alone; the dose and technic are essentially the same for all three stages, as the maximal doses of radiation are always employed.

The greatest recent advances in the treatment of cervical cancer have followed the adoption of some type of fractionated prolonged roentgen therapy, modified from the Coutard technic. This principle includes such factors as an increased target-skin distance (of 70, 90 or even 100 cm.), heavier filtration (1 mm. of copper) and daily repeated small doses (from 200 to 250 roentgens) to multiple pelvic portals (from 6 to 8) over a period of three weeks. Several ports are treated daily, alternating around the pelvis until each port receives from 1,800 to 2,100 roentgens. These measures have enabled the roentgenologist to give a larger depth or tissue dose to the cancer and to realize to the utmost the difference in radiosensitivity of the cancer and the intervening normal tissues, on which successful radiation therapy depends. The bulky, exophytic, papillary cancer may regress almost completely after the cycle of roentgen treatments so that the subsequent and supplementary radium therapy is considerably simplified. If it does not diminish greatly, it is my practice to excise it by means of an insulated endotherm loop snare. This avascular procedure has certain advantages to commend it; it removes the infected sloughing portion of the tumor; it permits the intra-uterine radium tandem to be placed in closer approximation to the base of the tumor and thus delivers a more effective dose, and finally it lessens the dose of intravaginal irradiation to be directed against the cervix.

The vaginal radium applicator to fit against the cervix to irradiate it and the parametrium is known as the Curie colpostat.<sup>22</sup> It consists of two corks mounted on a flexible steel strip covered by rubber tubing. Each cork is 1.5 cm. broad and 2.5 cm. long, so that with the radium-containing capsule within its interior more than 0.5 cm. wall of cork is left on either side. The ends of the corks are sealed with plugs. The apparatus is introduced into the vaginal fornices without anesthesia and is so directed that only the ends of the capsules are toward the rectum and bladder, the broad radiating surfaces facing the cervix and parametrial tissues. Additional radium-bearing corks may be adjusted within the concavity of the colpostat. A total dose of from 2,000 to 3,000 milligram hours is given with this applicator in addition to the intra-uterine dose. The filter is the equivalent of 1 mm. of platinum. If the uterine canal is impermeable, the treatment is made at two successive times, the vaginal applicator first (colpostat) and the uterine applicator later, after regression of the neoplasm has disengaged the canal. With only a small quantity of radium available these treatments are necessarily given in succession rather than simultaneously (fig. 20).

22. Regaud, C.: *Traitement des cancers du col de l'utérus par les radiations*, Cong. de la Soc. internat. de chir., Rep. 1:35-146, 1926.

The platinum capsules used in the colpostat have a wall thickness of 0.3 mm. of platinum. Each capsule is loaded with four of the unit cells of 3.33 mg. radium content each. This brings the total filtration value to 0.5 mm. of platinum. The platinum capsule or tube is now introduced into a heavy brass capsule of such wall thickness as to add an additional value of 0.5 mm. of platinum, making a total filtration of 1 mm. of platinum. If three capsules are employed, each containing four cells, or 13.3 mg. of radium, the total content of the colpostat would be 40 mg. With this intensity, a dose of 3,000 milligram hours would require seventy-five hours.

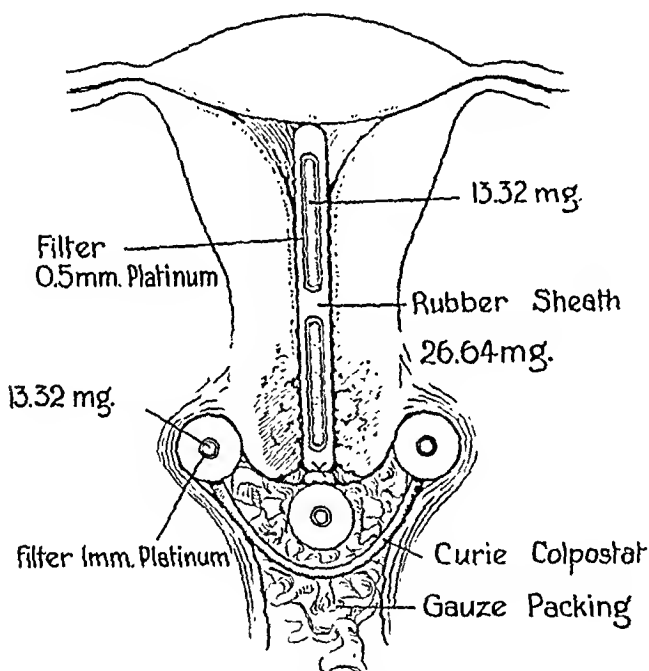


Fig. 20.—Distribution of radium in the treatment of carcinoma of the cervix uteri. In the uterine tandem the cervical capsule has twice as large a content of radium as the one in the fundus. The radium-bearing capsules in the colpostat have twice the filtration that is used in the uterine tandem.

In lieu of the Curie colpostat, the vaginal bomb as used by Healy at the Memorial Hospital may be substituted. This instrument (fig. 20) is applied against the cervix and toward the parametrium on each side. Its position is maintained by an adjustable upright standard attached to a "bomb board" with knee rests, which may be placed in the patient's bed. All the available radium (130 mg. in this instance) in platinum cells is placed within the cavity of the bomb. The filter consists of 0.2 mm. of platinum, 1 mm. of brass and 1 mm. of steel. The bomb has a circular surface with a diameter of  $1\frac{1}{2}$  inches (3.8 cm.). The dose is from 1,200 to 2,500 milligram hours, depending on whether



the application is in a single direction, e. g., central, or toward the parametrium on each side. This applicator can seldom be tolerated for more than five hours daily, as it is introduced without anesthesia. The treatment is completed in from two to four days (fig. 21).

The last and most important step in the treatment of carcinoma of the cervix is the insertion of an intra-uterine (and intracervical) tandem of radium capsules. The depth of the uterine cavity is measured by a sound in order to plan the length of the rubber tube containing the

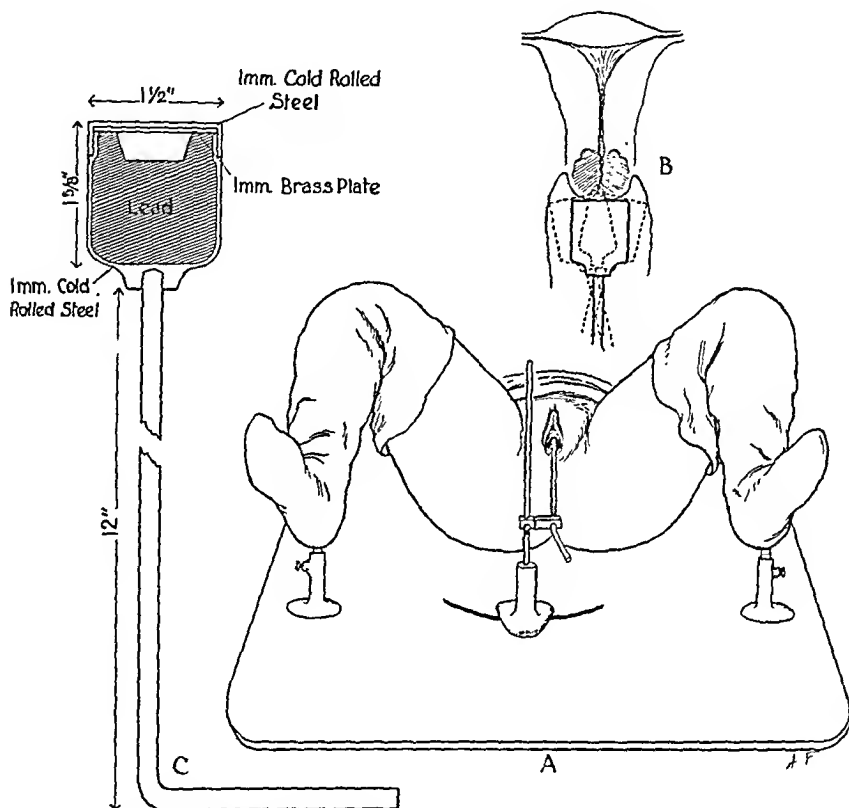


Fig. 21.—Radium bomb (C) for vaginal irradiation directed toward the cervix and parametria (B). In A the patient is shown in bed, resting on a specially designed board, with knee rests and adjustable bomb support, which permits the direction of the bomb to the center, right or left of the cervix. This apparatus is an exact model of the type used by Healy, of the Memorial Hospital.

radium. It is most essential for the entire length of the uterine cavity to be filled with radium capsules in tandem, otherwise the fundus will not scar and contract later, in which event pyometra may result. This tandem of radium capsules may be introduced in many patients without the use of an anesthetic if graduated Hegar sounds are used for the cervical dilatation. The filter of the intra-uterine capsules is 0.5 mm. of platinum. There are usually two capsules, a lower one in the cervical

canal and an upper one in the fundal cavity. The cervical capsule or tube contains eight of the unit cells of 3.33 mg. each (26.64 mg.), and the capsule or screen in the uterine cavity contains only four of these cells (13.32 mg.). Thus it is planned for the cervix to receive twice the dose that is given to the corpus uteri (fig. 20).

The radium within the uterus and vagina may require from three to five days in order to furnish the necessary sterilizing dose, but each morning these applicators are removed and sterilized while the patient is receiving a douche and then are reintroduced. The end-results in terms of five year cures are approximately the same whether the radium therapy is given intensively in from twelve to eighteen hours or continuously for five days, but the pliability and integrity of the vaginal vault are immeasurably better with the longer treatment. The intra-uterine dose is from 3,000 to 3,600 milligram hours; the latter dose is given only when the cavity of the body of the uterus is so long as to require two of the weaker radium capsules in addition to the more intensive irradiation within the cervical canal. The cautious radiologist will attempt to prevent undue irritation of the bladder and rectum by packing the anterior and posterior vaginal fornices tightly while the radium is in situ. This pushes these labile organs as far away as possible from the source of radiation and tends to prevent ulceration and the formation of fistulas.

*Cancer of the Body of the Uterus.*—Once carcinoma of the body of the uterus is diagnosed, the decision as to the method of treatment depends not only on the stage of the disease, i. e., technically operable or inoperable, but also on the histologic grade of the neoplasm. The anaplastic corporeal cancer of grade 4 is treated solely by radiation therapy even when in an operable stage. Cancers of the corpus of grades 1 to 3 are treated by radical panhysterectomy after intra-uterine radium therapy; roentgen irradiation in these cases is reserved for post-operative use.

The technic for irradiation of the inoperable cancer and the operable cancer of grade 4 is as follows: Preliminary high voltage roentgen therapy is given to four pelvic ports (sometimes six, to include lateral fields), the fractionated principle being employed, as for carcinoma of the cervix. An occasional disadvantage after such treatment is that the uterine canal may be so small that the subsequent introduction of radium is difficult. Emphasis is placed on the intra-uterine tandem of radium capsules. The filter of these capsules is the equivalent of 0.5 mm. of platinum (0.3 mm. of wall and 0.2 mm. for the enclosed platinum cells). There are usually three capsules, each containing four of the unit cells of 3.33 mg. each (13.32 mg.). The intra-uterine dose is from 3,600 to 4,000 milligram hours, more commonly the first.

Six weeks later a curettage is done for diagnostic purposes, and if viable carcinoma is found in the material obtained intra-uterine radium therapy is repeated, a smaller dose being used. If panhysterectomy is to be done, the operation is delayed until six weeks have elapsed after the completion of the preoperative irradiation.

*Malignant Tumor of the Ovary.*—Surgical removal of a tumor of the ovary is indicated because the clinician cannot always tell preoperatively whether the tumor is benign or malignant. The accepted treatment for malignant ovarian tumor is panhysterectomy. In some cases it has been thought wise to do a bilateral salpingo-oöphorectomy, the uterus being left in place to serve as a holder for radium. If the panhysterectomy removes all the clinical evidence of cancer, the patient nevertheless receives a prophylactic pelvic cycle of high voltage roentgen rays, consisting of 300 roentgens daily alternating to each of four or six ports until 2,000 roentgens are delivered to each field. A target-skin distance of 70 cm. is used. If peritoneal carcinosis is found at laparotomy, the primary tumor and the opposite ovary are removed if possible, as the carcinomatous implants and metastases have been known to disappear or regress or become inactive at the cessation of ovarian stimulation. If the ovarian carcinoma is manifestly inoperable at the time of diagnosis, roentgen therapy should be given. These treatments may cause the tumor to regress and become sufficiently mobile to permit later surgical removal, possibly resulting in better palliation. Healy emphasized the importance of irradiating the abdominal scar in all of these cases because of the danger of implants if removal of the malignant tumor is done.

For inoperable ovarian carcinoma additional radiation may be given by an intra-uterine tandem of three radium capsules for a dose of 4,000 milligram hours. The filter of these capsules is equivalent to 1 mm. of platinum, which affords a shorter and more penetrating gamma ray than is customarily used in the case of uterine cancer. If external irradiation is relied on as a sole method of treatment, the dose in roentgens delivered to each skin port by the fractionated method is increased to as high as 2,500 roentgens.

*Cancer of the Breast.*—The treatment of choice for operable carcinoma of the breast is radical amputation. Radical mastectomy is preceded by roentgen irradiation only when the carcinoma is on the borderline of operability; when the degree of malignancy—as judged by the clinical index—is high, and in young women when metastases are present in axillary nodes. This operation is one of the most successful in the field of cancer surgery; local recurrence develops in less than 10 per cent of cases, and then usually when the operation was ill chosen. The failure of the operation to cure the patient is usually due not to local recurrences but to distant metastases. Postoperative roentgen therapy is advised for

as a routine, for it is believed to decrease the incidence or at least delay the appearance of local recurrences. The methods of radiation therapy are not exact enough as yet to justify their routine substitution for radical mastectomy. Primary operable mammary cancer is treated by irradiation alone under two conditions: (a) when operation is contraindicated by the poor general condition of the patient and (b) when operation is flatly refused. Every recurrent and inoperable carcinoma is treated by irradiation, usually a combination of roentgen rays and thorotrast radium. The criteria of inoperability are based on the presence of any one of the following conditions: inflammatory carcinoma, carcinoma in the lactating breast (carcinoma mastitoides), fixation of tumor, fixation of axillary nodes, metastatic involvement of supraclavicular nodes or nodes in the opposite axilla, invasion of the opposite breast, marked extension into the skin and metastasis to the lungs, liver, bones, etc.

Carcinoma situated in the breast has certain physical advantages for the treatment by irradiation.<sup>23</sup> The mammary gland is superficial enough so that any tumor in its depth may receive a considerable percentage of the energy from external sources of radiation. The mobility of the breast permits a reasonably correct measurement of the tumor, an accurate estimation of the dosage and the proper implantation of radioactive foci. The reactionary phenomena after treatment of the breast are of little moment and are seldom complicated by sloughing and infection. The loss of mammary function is insignificant to patients with carcinoma of the breast, since their average age is slightly over 50 years.

Opposed to these advantages are certain disadvantages. The skin is not a successful irradiation of cancer of the breast. The skin is generally relatively radioresistant.<sup>24</sup> The thick skin of the breast is an extremely poor reactive tissue bed, with a poor capacity for the way of productive inflammation and fibrosis which is necessary for the carcinoma by irradiation. The delicate and thin skin of the axilla and sulcus of the breast will not tolerate much irradiation. The skin of the breasts in many cases metastasizes and therefore the use of irradiation is instituted.

Previous communications from the [redacted] detail a new method of treating [redacted] doses of radiation, delivered from [redacted] and by interstitial deposition of [redacted]

23. Lee, B. J.; Pack, G. T.; Quinn, J. W.: *Ann. Surg.* **94**:339-410 (March) 1932.

24. Stewart, F. W. Radiosensitization of  
(Dec.) 1933.

dose by physical and clinical experimentation has been determined as 10 threshold erythema doses. The depth dose which reaches the tumor from external sources of radiation was added to the interstitial dose. The accurate placement of interstitial radium in proper dosage can effect complete destruction of the mammary cancer, as has been demonstrated by clinical experimentation and subsequent microscopic study of the breast after amputation.<sup>25</sup>

The entire glandular system of the breast is condemned in certain varieties of mammary cancer. Diffuse ductal cancer involves the ducts in almost every lobule of the breast. Every duct is a potential site of cancer origin in the case of Paget's disease of the nipple. Even the localized carcinoma is accompanied by precancerous changes in the ducts of other lobules. I have occasionally seen multiple discrete cancers in the same breast; their multicentric origin can be attributed to a common underlying predisposition to cancer existent throughout the entire breast. In the majority of cases of cancer of the breast, infiltration of cancer cells extends beyond the palpable limits of the tumor. In such instances the palpable tumor may be completely devitalized by accurate interstitial irradiation, yet recurrence may appear later in a part of the breast peripheral to the original tumor. The factors enumerated above suggest a requirement of the utmost importance. The breast and the adjoining regions of lymphatic drainage must receive diffuse rather than focal irradiation, and the dose must be lethal for cancer cells in any environment.

If a mammary cancer is to be treated solely by radiation therapy, the following technic is employed. After confirmation of the diagnosis by aspiration biopsy, the breast, axilla and supraclavicular space are treated by high voltage roentgen therapy. The five skin portals commonly used are the median side of the breast, the lateral side of the breast, the axilla direct, the axilla posterior and the supraclavicular space, the latter field including the superior part of the breast and the anterior axilla. The beam is directed tangentially to the wall of the chest to avoid as far as possible the danger of late pulmonary fibrosis. Two fields are treated daily at 50 cm. target-skin distance with doses of 250 roentgens each. Treatments are alternated daily until each field receives from 1,500 to 1,750 roentgens. The external irradiation is followed immediately by the insertion of radium needles.

The breast and axilla are prepared as for any surgical operation. Anesthesia is induced and maintained as a rule by the intravenous administration of the sodium salt of normomethylcyclohexenylmethylmalonylurea. The introduction of the radium needles is facilitated by

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25. Lee, B. J., and Pack, G. T.: Irradiation of Mammary Cancer with Special Reference to Measured Tissue Dosage, *Acta radiol.* 12:416-454, 1931.

puncturing the skin with a small pointed knife (no. 11 Bard-Parker blade). The dose to be given by interstitial radium therapy is calculated by subtracting the tissue dose delivered by the roentgen rays from the known cancerocidal dose of from 6 to 10 threshold erythema doses. The number of millicuries destroyed or milligram hours may then be ascertained by consulting table 4. The size and position of the tumor as well as the relative size of the breast influence the arrangement and distribution of the needles. The radial arrangement of Keynes is suitable for the small cancer which is centrally situated.<sup>26</sup> A larger tumor necessitates the placement of the needles in a series of parallel rows or even in gridiron formation.<sup>27</sup> The needles surround the tumor in most instances, as there is some suspicion that insertion into the carcinoma

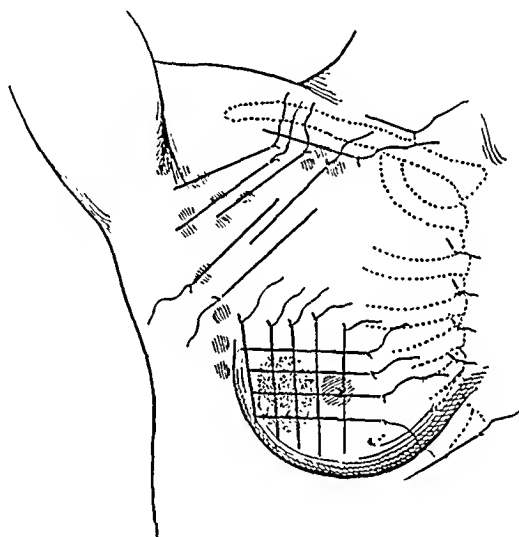


Fig. 22.—Distribution of radium-bearing needles in the breast, axilla, supraclavicular space, epigastrium and parasternal intercostal spaces. The sheath needles vary in length and contain from one to four of the small radium cells placed end to end.

itself involves the risk of transplanting or disseminating the cancer. As the main lymphatic channels run deep to the breast in the pectoral fascia, the greatest concentration of interstitial irradiation is rightly in this plane; this also avoids excessive irradiation to the skin, a complication which may follow the too superficial implantation of radium needles. Keynes has always stressed the point that a gap of untreated breast should not be left between the tumor and the anterior fold of the axilla.

26. Keynes, G.: (a) The Treatment of Primary Carcinoma of the Breast with Radium, *Acta radiol.* **10**:393-402, 1929; (b) Radium Treatment of Carcinoma of the Breast, *Lancet* **1**:439-442 (March 1) 1930.

27. Pack, G. T.: The Interstitial Use of Gold Filtered Radon Transfixion Tubes in the Treatment of Mammary Cancer, *Am. J. Roentgenol.* **27**:532-546, 1932.

The total dose in the breast varies from 40 to 80 millicuries destroyed. The needles may be of the long sheath variety, containing four of the platinum cells in tandem, or shorter needles holding only two radium cells may be used.

In the axilla, the radium needles are inserted fanwise in order to afford diffuse and accurate irradiation to the axillary contents. They are introduced from below upward or downward from the infraclavicular region, care being taken to avoid the neurovascular bundle at the apex of the axilla. The insertion is made with the arm in abduction. The axillary needles form a pyramidal pattern, which is really the shape of the axilla. A dose of 35 millicuries destroyed can be given safely in the axilla by this method. This irradiation is supplemented by the introduction of radium needles in the infraclavicular region after the plan of Keynes. The needles are plunged directly backward to pierce the pectoral muscles and impinge on the points of the needles introduced directly through the axilla.

Additional needles are placed deeply in the paramammary region, where the principle of a circumferential barrage is employed. One needle extends diagonally across the junction of breast and epigastrium and another lies along the lowermost border of the pectoral fold. Two single cell needles are inserted in the supraclavicular space parallel to the middle third of the clavicle. A Treves needle containing one radium cell is inserted into each of the upper three intercostal spaces in an attempt to block the lymphatic vessels which enter the mediastinum in this location. These needles are placed very close to the sternal margin in order to avoid injury to the internal mammary artery. The dose is never greater than 2 millicuries destroyed for each radium cell. The attached threads for the withdrawal of the needles are tied snugly across the breast and thereby maintain the position of the implants. The arm is kept in abduction while the needles are in place, as this position prevents undue irradiation of the brachial plexus and consequent neuritis. A diagram for the record is made of the arrangement of the radium and the location and dose delivered by each needle. The duration of the interstitial irradiation is from five to seven days, although it may vary more or less. Extraction of the needles can usually be accomplished without anesthesia.

The pursuance of this plan of treatment will meet with some success. It is so conceived that it should destroy any mammary cancer so treated, were it not for unavoidable technical errors. The dose delivered is epidermicidal, and the vesication and injury to the skin are responsible for a long convalescence and considerable distress.

# THE HYDRODYNAMICS OF THE RELIEF OF DISTENTION IN THE GASTRO-INTESTINAL TRACT BY SUCTION APPLIED TO INLYING CATHETERS

JOHN RANDOLPH PAINE, M.D.

MINNEAPOLIS

## INTRODUCTION

The clinical use of nasal catheter suction-siphonage on over two thousand patients presenting a great variety of pathologic conditions at the University Hospitals during the past four years has amply proved how distention and stasis in the stomach and small intestine may be satisfactorily controlled.<sup>1</sup> The technic of its application and the indications and contraindications for its use as well as the results which may be achieved have been reported.<sup>2</sup>

In the following thesis an attempt is made to elucidate some of the mechanicophysilogic principles concerned and the manner in which distention is prevented or preexisting distention is relieved by the use of this method.

*Historical Background.*<sup>3</sup>—The use of tubes inserted through the esophagus to relieve gaseous distention probably dates from 1767, when Alexander Monro II, of Edinburgh, employed a flexible tube of coiled wire covered with leather to remove fermenting fluids and gases from the stomachs of cattle.<sup>4</sup> Exactly a hundred years passed before this method of treatment was applied to human beings. Adolf Kussmaul<sup>5</sup> in 1867 made a diagnosis of gastric dilatation due to pyloric ulcer in the case of Marie Weiner. She was successfully treated by frequent empty-

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From the Department of Surgery, University of Minnesota.

Submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements of the degree of Master of Science in Surgery.

1. Paine, J. R.; Carlson, H. A., and Wangenstein, O. H.: Post-Operative Control of Distention, Nausea, and Vomiting: Clinical Study with Reference to Employment of Narcotics, Cathartics, and Nasal Catheter Suction-Siphonage, J. A. M. A. **100**:1910-1917 (June 17) 1933.

2. Wangenstein, O. H., and Paine, J. R.: Nasal Catheter Suction Siphonage: Its Uses and Technic of Its Employment, Minnesota Med. **16**:96-100, 1933.

3. Paine, J. R.: History of Invention and Development of Stomach and Duodenal Tubes, Ann. Int. Med. **8**:752-763, 1934.

4. Monro, A.: De dysphagia, Edinburgh, A. Neill & Socii, 1797, p. 83.

5. Kussmaul, A.: Ueber die Behandlung der Magenereiterung durch eine neue Methode mittelst der Magenpumpe, Deutsches Arch. f. klin. Med. **6**:455, 1869.



the difference in the heights of the columns of water in the adjacent loops. The difference in the heights of these columns of water was measured, and their sum was found to be 109 cm. of water. One hundred and nine divided by 13.6 (specific gravity of mercury) gives 8.01, the number of centimeters of mercury. Thus the experimental results checked with the theoretical result within the error of measurement (8.30 cm. of mercury compared to 8.01 cm. of mercury).

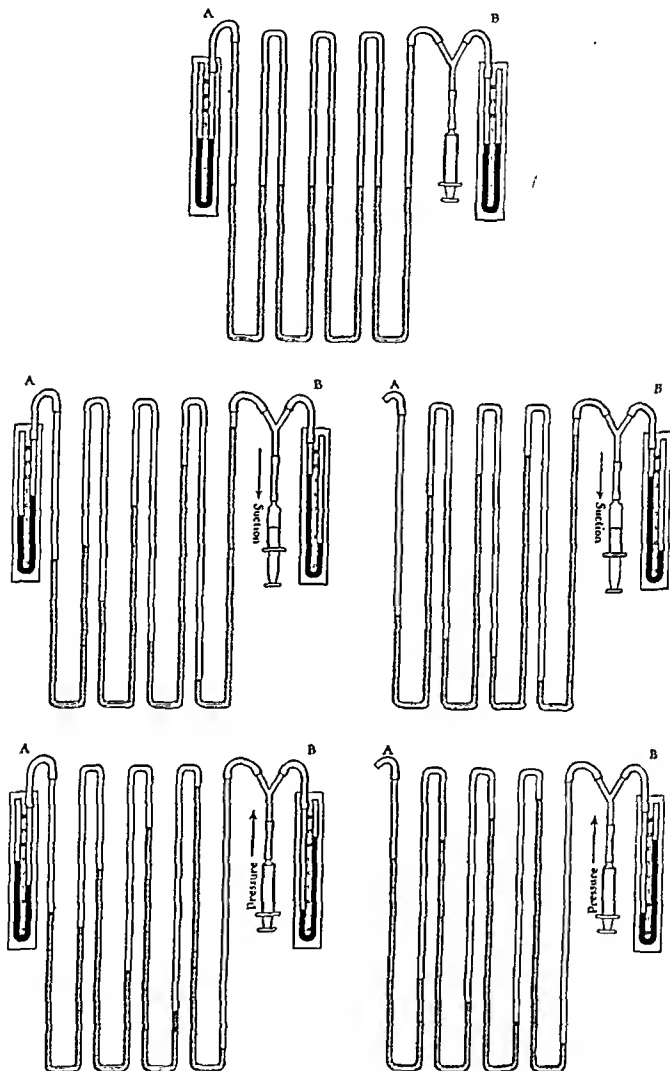


Fig. 1.—Loss in hydrostatic pressure when transmitted through a series of connected vertical rigid loops partially filled with fluid.

The same system of tubes was used again, but instead of applying suction at point *B*, a positive pressure equal to 13 cm. of mercury was used. The pressure at point *A* was found to be 4.4 cm. of mercury. This loss of pressure had again occurred as a result of the formation of unequal columns of water. When the foregoing experiments were repeated with point *A* open, different but analogous results were obtained. The pressure at point *A* in these experiments was the same

as that of the atmosphere, but the formation of unequal columns of water occurred as in the preceding experiments (fig. 1).

When the tubes were completely filled with water, air or an intimate admixture of fluid and gas, such as whipped cream, no loss of either positive or negative pressure occurred in transmission through the system. When whipped cream was used, however, it was observed that after a short time small quantities of liquid cream separated out and collected at the bottom of the loops. Under these circumstances small losses of both positive and negative pressure occurred in transmission through the system.

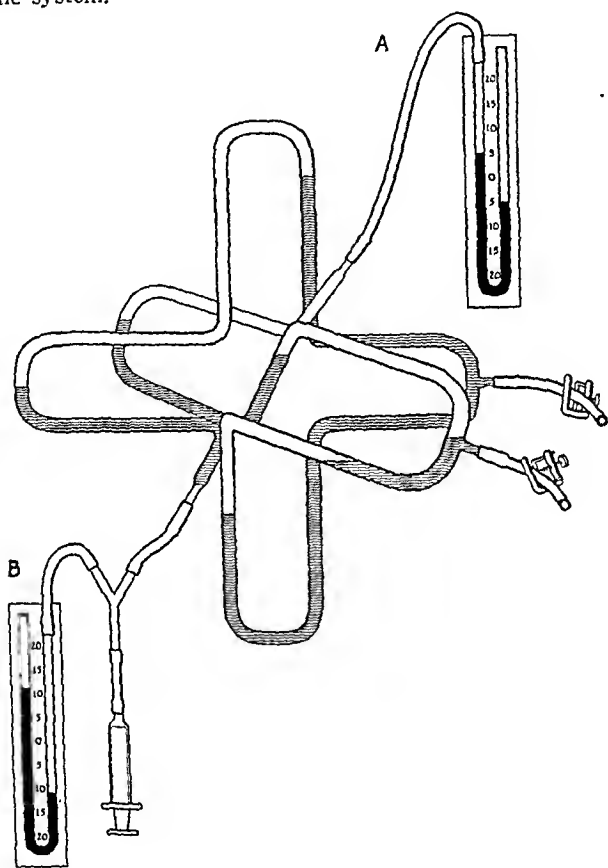


Fig. 2.—Difference in hydrostatic pressure at the two ends of a series of connected rigid loops occupying all three planes of space and partially filled with fluid.

If the tubes were filled as shown in figure 1 and then placed in a horizontal plane, the pressure at points *A* and *B* immediately became equalized, despite any unequal columns of fluid which might have been present before.

*Pressure Phenomena in a Rigid Tube with Connected Loops in All Three Planes of Space.*—The glass tube represented in figure 2 yielded some interesting observations. A certain amount of water was placed in the system so that about equal parts of water and air were present in each loop. Water manometers were then attached to each end, and the changes in pressure which occurred with movements of the whole apparatus were recorded. Needless to say, the relative position

of the water and the proportions of air and water in any one loop varied with the changes in position of the apparatus as a whole. The recorded pressures were as follows:

Position	A	B
	Cm. of Water	Cm. of Water
1	— 11.75	+ 3.0
2	— 8.25	+ 4.5
3	— 9.25	+ 4.5
4	— 11.50	+ 6.0
5	— 7.75	+ 11.0
6	— 5.25	+ 11.0

These figures show that it is possible to change the pressure at the ends of such a system simply by changing the relative position of the contents of the tube. It follows as a corollary that the changes in pressure are due to the varying quantities of fluid in vertical loops. By various successive changes of position of the whole apparatus, the pressures at the two ends could be finally equalized. It was noted that whenever this occurred all the fluid was in loops which were horizontal. The significance of these observations and the application of the principles which they represent in the decompression of the upper part of the gastro-intestinal tract by nasal catheter suction-siphonage will be discussed later.

#### MECHANICS AND PHYSICS OF THE NASAL CATHETER SUCTION-SIPHONAGE APPARATUS

*Description of Apparatus Used.*—The basic mechanical principle involved in nasal catheter suction-siphonage is the maintenance of a continuing negative pressure within a duodenal tube inserted into the stomach or duodenum. This negative pressure is produced and maintained by the use of two bottles with a capacity of approximately 4.5 liters each and a system of rubber tubes. One bottle is filled with water and fitted with a two-holed rubber stopper which contains two glass tubes. One of these glass tubes is short and extends just through the rubber stopper. The other is longer and extends almost to the bottom of the bottle. A length of rubber tubing about 5 feet (152 cm.) long leads from the short glass tube to the second bottle. Another length leads from the longer glass tube and is attached to the duodenal tube. The bottle filled with water is hung inverted from a standard, and enough water is placed in the other bottle just to cover the end of the rubber tubing attached to the shorter glass tube. A diagram of this apparatus is given in figure 3. It is readily seen that this apparatus comprises a modified form of siphon, the head of water held in the inverted bottle serving to make the siphonage action constant when

gas is aspirated through the duodenal tube. A negative pressure is created at the top of the inverted bottle because water tries to run out through the rubber tubing leading to the lower bottle. This negative pressure is transmitted through the longer glass tube and is sufficient to aspirate any gas or fluid in the vicinity of the end of the duodenal

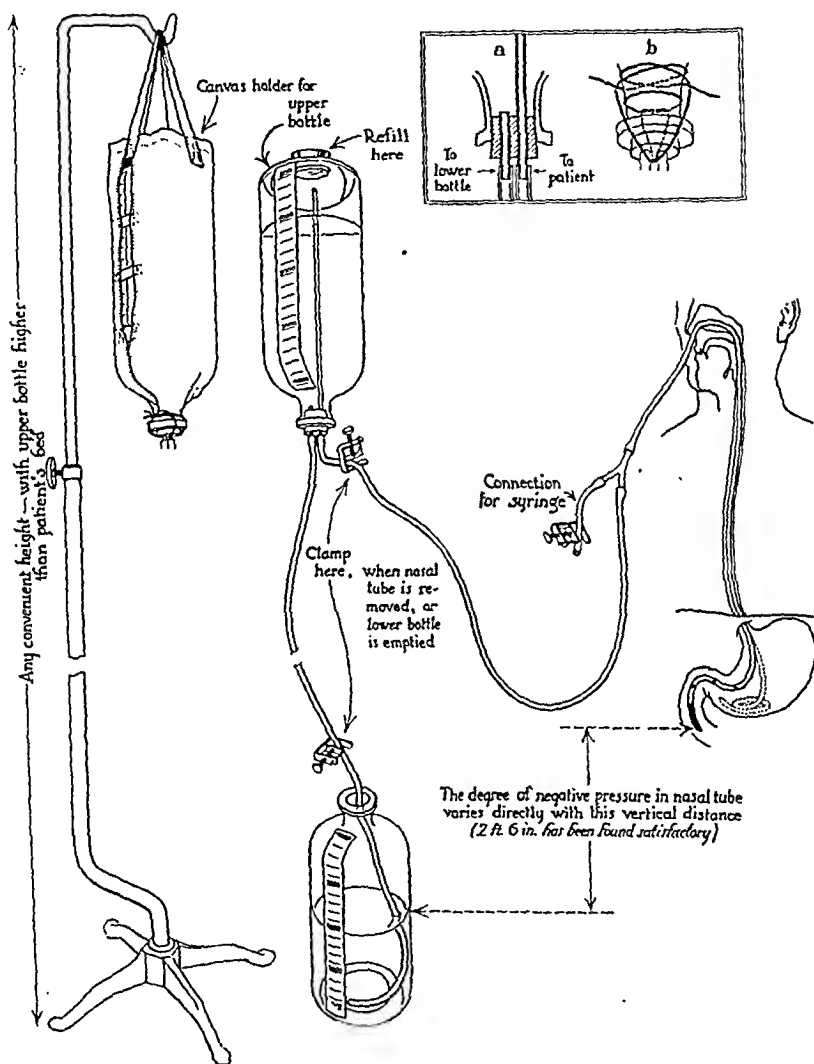


Fig. 3.—Diagram of the nasal catheter suction-siphonage apparatus used at the University Hospitals.

tube. This suction action occurs whether the free end of the longer glass tube is below or above the water level in the inverted upper bottle and whether or not fluid or gas is aspirated. If the longer glass tube does not project above the water level in the inverted bottle, however, the effective negative pressure transmitted to the duodenal tube will

be decreased by as many centimeters of water pressure as the end of the tube is below the water level.

If it be assumed that fluid alone is being aspirated, the exact mechanism by which suction occurs can be more easily seen. Under these circumstances two columns of water of unequal height are formed, the taller extending from the level of the water in the inverted bottle to the level of the water in the lower bottle and the shorter extending from the tip of the longer glass tube in the inverted bottle to the perforations in the distal tip of the duodenal tube. Since these columns of water are unequal in height and therefore produce unequal pressures, the shorter column is aspirated into the inverted bottle by the taller one.

While a negative pressure will be maintained as long as any water remains in the top bottle, the degree of negative pressure is dependent on various factors and is constantly changing within fairly wide limits. In practice, both fluid and gas in varying amounts are recovered by the apparatus. The degree of negative pressure transmitted to the duodenal tube varies directly with the proportion of gas present in that tube, the longer glass tube and the rubber tubing connecting them. Gas has little weight and allows the full effect of the column of water running from one bottle to the other to be exerted. As aspiration proceeds, the levels of water in the two bottles gradually shift since the lower bottle fills and the upper bottle empties. When this occurs the column of water which creates the negative pressure in the system is shortened, and consequently the suction exerted through the duodenal tube is decreased.

The actual degree of negative pressure created and the variations in it which occur with the changing conditions mentioned previously were measured in the laboratory by attaching a manometer to the distal end of the duodenal tube by means of a glass Y tube. Figure 4 is the graphic representation of these measurements. It will be noted that the greatest negative pressure which the apparatus will create is between  $-150$  and  $-160$  cm. of water and that this pressure results only when gas alone is being aspirated. When fluid is being aspirated, the greatest negative pressure which can result is between  $-65$  and  $-70$  cm. of water.

*Possible Modifications of the Apparatus.*—Several modifications of the apparatus are possible. Should a milder degree of suction be desired, the lower bottle which rests on the floor has merely to be elevated and placed on a stool or box. The height of the taller column of water is thereby shortened, and the effective negative pressure furnished by the apparatus is decreased by as many centimeters of water as the lower bottle is raised. On the other hand, increasing or decreasing the height at which the upper bottle is suspended will have no effect on the degree

of negative pressure furnished if fluid alone is being aspirated. However, if gas alone is being aspirated, the degree of negative pressure furnished will be increased or decreased by as many centimeters of water as the upper bottle is raised or lowered. When mixtures of gas and fluid are aspirated, the negative pressure varies between the limits set above, depending on the proportion of gas and fluid passing through the duodenal tube at any one time.

If the distance between the end of the duodenal tube and the level of the water in the lower bottle is increased by placing the patient's bed on blocks, the negative pressure furnished will be increased by as many centimeters of water as the bed is elevated. The greatest negative

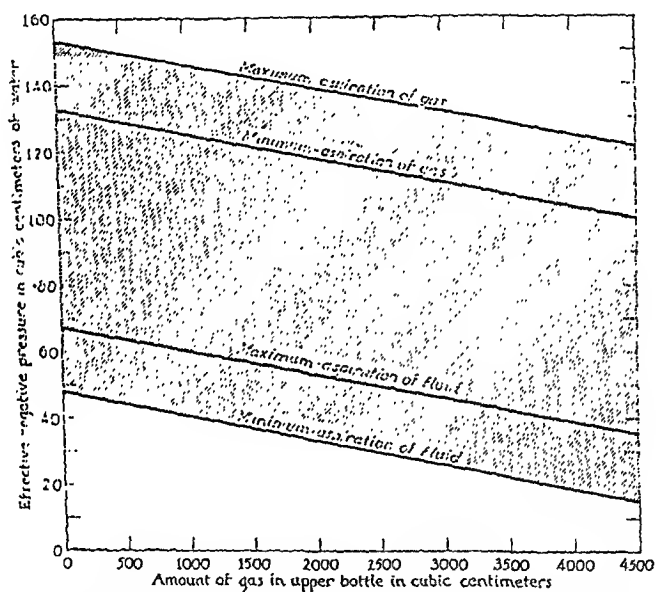


Fig. 4.—The effectual negative pressure created in the duodenal tube by the nasal catheter suction-siphonage apparatus. The variations in this pressure which occur are indicated. At any given time the effectual negative pressure will fall somewhere within the shaded area.

pressure that it is theoretically possible to create with such a system is about  $-1,000$  cm. of water. This limit in the degree of negative pressure is set by the atmospheric pressure. Should a greater negative pressure be required than can be conveniently provided by placing the patient's bed on blocks, two, three or more suction sets may be connected in series, as shown in figure 5. For experimental purposes my associates and I have employed such an arrangement on occasions but have found no benefit to accrue from its use. The duodenal tube itself will collapse with the negative pressure created by such a system, and there is a theoretical danger of necrosis of the mucosa of the stomach or bowel when exceptionally high negative pressures are used.

If a third bottle, as shown in figure 6, is interpolated between the duodenal tube and the inverted bottle, the negative pressure furnished by the apparatus becomes much less variable, and if this bottle is placed on a level with the distal end of the duodenal tube the variations in the negative pressure due to alternate aspiration of fluid and gas or a mixture of both will be practically entirely eliminated. We have frequently used this third bottle to catch aspirated fluid so that it could be returned

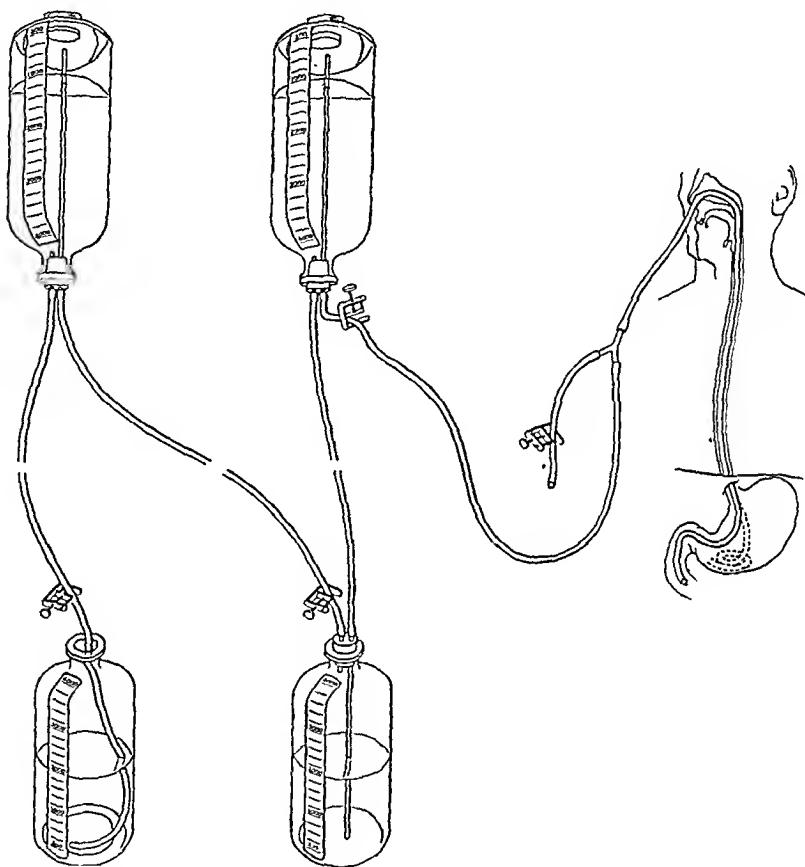


Fig. 5.—The arrangement by which the effectual negative pressure furnished by the nasal catheter suction-siphonage apparatus may be increased to any desired degree up to approximately 1,000 cm. of water.

to the patient in rectal irrigations to make up partially for the loss of fluid which occurs when nasal catheter suction-siphonage is used. This is always done in cases in which large fluid aspirations occur.

*Measurement of Aspirated Fluid and Gas.*—The amounts of fluid and gas aspirated by the suction apparatus can be easily calculated by simple arithmetic. The gas is collected in the inverted bottle, and its amount can be read directly from a calibrated scale attached to the bottle. Since no two substances can occupy the same space at the same time,

any fluid or gas which passes into the upper bottle must displace an equal volume of fluid in that bottle. The volume of the fluid in the lower bottle, therefore, must be equal to the sum of the volume of fluid which was in it at the beginning and the volume of the fluid and gas aspirated. Two of the three quantities being known, the volume of aspirated fluid is obtained by subtraction.

The amount of aspirated gas which is measured by the scale on the upper bottle is obviously not the true volume. After being aspirated

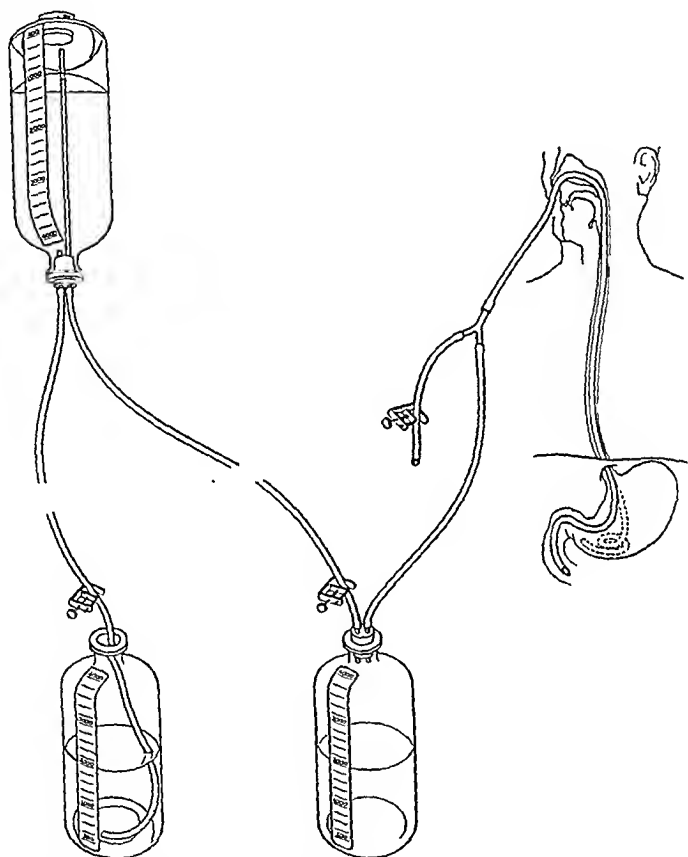


Fig. 6.—The arrangement by which the variations in the effectual negative pressure furnished by the nasal catheter suction-siphonage apparatus may be decreased and by which the aspirated fluid may be caught and returned to the patient as rectal injections if desired.

from the body, the gas decreases in volume owing to the change in temperature which occurs. The gas as it is contained in the upper bottle, however, is constantly at a greater negative pressure than it could possibly be within the gastro-intestinal tract.

If it is assumed that the patient's temperature is 98.6 F., that the pressure of the gas in the intestine is  $+12$  cm. of water pressure and that the gas as contained in the suction apparatus is under  $-150$  cm.



of water negative pressure, it can be calculated that 1,000 cc. of gas as read on the calibrated scale of the suction bottle represents only 892 cc. of gas removed from the patient. Thus the readings are in error by approximately 10 per cent. It is unlikely, however, that this error would ever be of great importance. The difference between the actual volume and the measured volume is relatively insignificant for all clinical purposes.<sup>16</sup>

16. The following is the method by which the amounts of gas and fluid aspirated by the apparatus are calculated.

Readings of fluid levels by the attached calibrated scales when aspiration is begun:

Upper bottle	0 cc.
Lower bottle	400 cc.

Readings of fluid levels after a given period of aspiration:

Upper bottle	1,400 cc.
Lower bottle	2,300 cc.

Gas aspirated is measured directly by reading the fluid level of the upper bottle, i. e., 1,400 cc.

Fluid aspirated is obtained by subtracting 1,400 and 400 cc. from 2,300 cc., i. e., 500 cc.

1,400 cc.	2,300 cc.
+ 400 cc.	— 1,800 cc.
<hr/>	<hr/>
1,800 cc.	500 cc.

Wangensteen has found by actual measurement at operation that the pressure of gas in the distended small bowel of patients with intestinal obstruction varies from +8 to +24 cm. of water. Plus 12 cm. is the average pressure found. Slight variations in the intra-intestinal pressure affect the calculated results insignificantly.

Formula to calculate corrected volume of aspirated gas:

$$\frac{VP}{T} = \frac{V'P'}{T'}$$

V indicates the volume of gas in cubic centimeters as measured in suction apparatus; P, the pressure of gas in centimeters of water as contained in suction apparatus; T, the temperature of gas in degrees centigrade calculated from absolute zero as contained in suction apparatus; V', the corrected volume of gas in cubic centimeters; P', the pressure of gas in centimeters of water as present in patient, and T', the temperature of gas in degrees centigrade calculated from absolute zero as present in the patient.

In the example given above the calculation is as follows:

$$\begin{array}{r} 1,000 \times 883.6 = V' \times 1,045.6 \\ \hline 294 \qquad 310 \\ 883,600 = 1,045.6 V' \\ \hline 294 \qquad 310 \\ 3,005.44 = 3.37 V' \\ V' = 891.8 \end{array}$$

CHANGES IN PRESSURE IN THE SMALL INTESTINE WHEN A  
NEGATIVE PRESSURE IS CREATED AT ONE END OF IT

The experiments with rigid tubes forming a connected series of vertical loops had shown that an important factor which militated against the evacuation of such tubes with suction when they were partly filled with fluid was the rapid decrease in the force of suction due to the formation of unequal columns of fluid. Similar experiments were performed on the small intestine itself.

*Experiment on Human Small Intestine Removed at Autopsy.*—A complete small intestine was removed from a body at autopsy and arranged in a large pan to simulate as closely as possible the kinks and loops present in the living abdomen. The distal end was tied with tape around a glass tube which was connected to a water manometer. A duodenal tube was inserted into the proximal end for a short distance, and the intestine was tied around this with tape. Water and air were injected alternately through the duodenal tube in quantities of 50 cc., while the pressure developed in the distal portion of the intestine was noted on the manometer. Two thousand, two hundred and fifty cubic centimeters of water and an equal quantity of air were injected when the manometer recorded a pressure of  $+21$  cm. of water. The intestine was markedly distended and tense. Although the pressure at the proximal end was not measured, it was thought to be considerably higher than at the distal end, judging from the tenseness of the wall of the bowel. Further quantities of gas and water were then injected until a pressure of 33 cm. was finally built up in the distal portion of the intestine. The contained gas and water were then allowed to escape of their own accord through the duodenal tube. The pressure at the distal end as recorded by the manometer, however, fell to only  $+27$  cm. of water. With the application of suction to the duodenal tube an additional large amount of gas and fluid was removed from the intestine, and the 8 inches (20.3 cm.) of the duodenum adjacent to the duodenal tube became entirely collapsed. The pressure recorded by the manometer fell to  $+18$  cm. of water.

*Experiments on Small Intestines of Anesthetized Dogs.*—The same experiment in a slightly more elaborate form was next carried out on nine dogs previously starved for twenty-four hours and anesthetized with pentobarbital sodium given intravenously. In these dogs the abdomen was first opened, and a tight tape ligature was placed around the terminal portion of the ileum. Just above this ligature a glass tube connected to a water manometer was placed in the bowel. A duodenal tube was then inserted into the duodenum, and the bowel was tied closely around it with tape. Varying quantities of air were injected through the duodenal tube in five of the dogs and air and water in four. The hydrostatic pressure which the manometer recorded was noted, and then suction was applied to the duodenal tube. The same degree of negative pressure that is used clinically was employed. The change in the manometer reading gave the effect of the suction as transmitted through the length of the bowel. The segment of intestine immediately adjacent to the tip of the duodenal tube immediately became collapsed and entirely empty of both fluid and gas soon after the application of suction. Table 1 presents the results of these experiments in tabulated form. It is to be noted that in only one instance did the pressure in the terminal ileum become zero, and in that instance the intestine had been distended with air alone. This is significant.

*Air Traps and Pressure Gradients.*—From table 1 it is seen that the average decrease in pressure in the terminal portion of the ileum

was slightly better when gas alone was used to distend the bowel than when both gas and water were used. This difference appeared to be due to the division of the water contained in the bowel into unconnected portions and the consequent formation of air traps. The inability to reduce the ileal pressure consistently to zero when gas alone was employed to distend the bowel appeared to be due to the kinking of the bowel at irregular intervals as it lay in the abdominal cavity.

Additional evidence that kinks and air traps in the bowel prevent the free transmission of hydrostatic pressure along the length of the

TABLE 1.—*Immediate Pressure Changes in the Terminal Portion of the Ileum of Dogs After the Application of from 70 to 150 Cm. of Water Negative Pressure to a Duodenal Tube in the Duodenum\**

Dog	Amount of Water and Air Used to Distend Small Intestine, Cc.		Amount of Water and Air Removed from Distended Small Intestine by Suction, Cc.		Pressure in Terminal Portion of Ileum, Cm.		Percentage Decrease in Pressure of Terminal Ileum Due to Suction
	Air	Water	Air	Water	Before Application of Suction, Water	After Application of Suction, Water	
1	120	...	...†	...	8.0	2.5	69.0
2	100	...	70	...	9.6	0.0	100.0
3	250	...	150	...	26.5	10.0	62.0
4	300	...	225	...	28.0	5.0	82.0
5 a	560	...	235	...	76.2	35.4	53.0
b	535	...	375	...	81.6	29.9	63.0
Average.....					38.3	13.8	71.5
6	300	800	60	125	19.0	14.0	26.0
7	...†	...†	...†	...†	38.0	14.0	63.0
8	75	500	0	225	56.0	15.0	73.0
9	450	200	...†	...†	70.0	5.0	93.0
Average.....					45.8	12.0	64.0

\* All dogs were previously starved for twenty-four hours. For all practical purposes the small intestine was empty.

† Quantities not measured.

intestine was found in experiments of a similar nature in which the intra-enteric pressure was measured by manometers at different places along the bowel. If quantities of air, water or both are injected at one end of the small intestine, a gradient of pressure will be found, the pressure tending to decrease as the point of measurement becomes further removed from the source of the injection. The reverse of this is also true. Given a bowel distended with air, water or both and apply suction at one end. Measurements of pressure at intervals along the bowel starting near the point of suction will show an increasing gradient of pressure. These facts were found to be true by experiments on six dogs anesthetized with pentobarbital sodium injected intravenously. These dogs were all starved for twenty-four hours before the experiments so that their small intestines were empty and collapsed. A lapa-

rotomy was performed, and the terminal portion of the ileum was occluded with a tape tie. A duodenal tube was then passed through the stomach and into the duodenum. The duodenum was tied around the tube by means of tape. Air and water were injected into the intestine either through the duodenal tube or by means of fine needles inserted obliquely through the wall of the bowel. A negative pressure of from 70 to 150 cm. of water was created in the duodenal tube when desired

TABLE 2.—*Pressure Gradients in the Distended Small Intestine of Dogs*

Dog		Pressure in Cm. of Water		
		Duodenum	Jejunum	Ileum
10	80 cc. of air injected into ileum.....	14.6	12.5	24.8
	Three hours later.....	2.0	7.0	0.5
	30 cc. of air injected into duodenum.....	9.0	7.5	8.0
	Suction applied to duodenal tube.....	2.0	3.0	2.5
11	100 cc. of air injected into duodenum.....	27.2	0.0	0.0
	Eight minutes later.....	26.0	8.1	16.3
	Eleven minutes later.....	25.0	10.0	15.0
	200 cc. of air injected into duodenum.....	32.6	8.1	19.0
	100 cc. of air injected into duodenum.....	32.6	27.2	21.8
	200 cc. of air injected into duodenum.....	32.6	35.4	38.1
	200 cc. of air injected into duodenum.....	54.4	43.5	43.5
	Air allowed to escape through duodenal tube.....	0.0	13.6	21.8
12	100 cc. of air injected into duodenum and 50 cc. of air injected into jejunum			
	Thirty minutes later.....	38.0	27.0	38.0
	50 cc. of air injected into duodenum.....	81.6	43.5	46.2
	200 cc. of air injected into duodenum.....	84.3	76.1	81.6
	Suction applied to duodenal tube (375 cc. of air aspirated) .....	16.3	19.0	29.9
	400 cc. of air injected into duodenum.....	76.2	68.0	76.2
	Suction applied to duodenal tube (350 cc. of air aspirated) .....	16.6	20.4	35.4
13	50 cc. of air injected into ileum.....	7.0	10.6	10.4
	Fifteen minutes later.....	0.6	4.6	0.8
	50 cc. of air injected into ileum (15 minutes later).....	4.0	7.0	9.6
	Suction applied to duodenal tube.....	0.0	2.6	0.0
14	800 cc. of water and 300 cc. of air injected alternately in small quantities into duodenum.....	12.0	11.2	0.6
	Suction applied to duodenal tube (125 cc. of water and 60 cc. of air aspirated).....	6.2	7.4	0.4
15	50 cc. quantities of air and water injected alternately into duodenum until.....	38.0	....	30.0
	Suction applied to duodenal tube.....	0.0	0.0	14.0

by connecting it to a suction apparatus. Intra-intestinal pressures were measured by inserting a needle connected to a water manometer obliquely through the wall of the bowel. One of these experiments is reported in detail. A summary of the results obtained on the six dogs appears in table 2.

*Experiment on the Distended Small Intestine of a Dog, Showing Formation of Pressure Gradients.*—A mongrel dog weighing 17 Kg. and previously starved for twenty-four hours was anesthetized with 35 mg. of pentobarbital sodium per kilogram injected intravenously. Laparotomy was performed, and the bowel was

arranged to hang over the side of the animal, as shown in figure 7. The bowel measured 140 cm. in length. The terminal ileum was tied with tape. A duodenal tube was inserted through the stomach into the upper part of the jejunum and held in place with a tape tied around the bowel. Air and water were injected alternately in quantities of 50 cc. through the duodenal tube. Pressures were measured by puncturing the bowel obliquely with a small needle attached to a water manometer. A pressure of 30 cm. of water was finally built up in the distal end of the intestine. The pressure in the proximal portion was 38 cm. of water. From 70 to 150 cm. of negative pressure was applied to the duodenal tube. The pressure in the distal portion of the intestine fell to 14 cm. of water and remained constant. The proximal 10 cm. of the intestine became completely collapsed. Pressures were then measured along the course of the intestine as shown in figure 7.

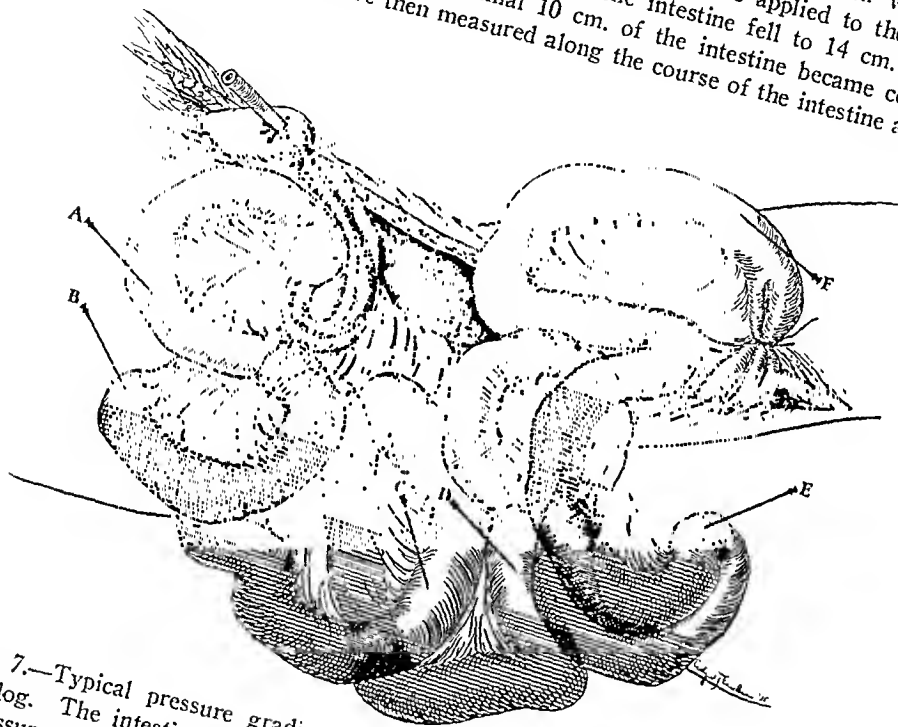


Fig. 7.—Typical pressure gradient occurring in the distended small intestine of the dog. The intestine has been filled partly with water and partly with air. The pressures at *A* and *F* before the application of suction to the duodenal tube were plus 38 cm. of water and plus 30 cm. of water, respectively. After the application of suction to the duodenal tube pressures in centimeters of water were recorded as follows: *A*, 8 cm.; *B*, 10 cm.; *C*, 10 cm.; *D*, 12 cm.; *E*, 15 cm., and *F*, 14 cm.

#### OBSERVATIONS ON THE PHYSIOLOGIC MECHANISM OF DECOMPRESSION OF THE SMALL INTESTINE OF CATS WITH NASAL CATHETER SUCTION-SIPHONAGE

In order partially to visualize what occurs in the distended human abdomen when suction is applied to a duodenal tube lying in the stomach or duodenum, observations were made on seven cats. In five of these animals a negative pressure equivalent to that used clinically was

employed. In the other two animals a negative pressure about one-half as great as that used clinically was employed.

*Technic of the Experiments.*—The observations were made as follows: Surgical anesthesia was obtained by the intraperitoneal injection of pentobarbital sodium. A laparotomy was performed, and the small intestine was measured. A duodenal tube was then passed into the stomach or through the stomach into the duodenum. The size of the intestine and any distention due to gas or fluid were noted. Quantities of air varying from 25 to 80 cc. were then injected into the intestine by means of a fine needle and syringe. The point of injection was varied from time to time. The abdomen was then closed, and suction was applied to the duodenal tube. After from one-half to two hours, the amount of gas aspirated was recorded, and the abdomen was reopened. The intestines were reinspected for changes in the disposition of the gas and the degree of decompression which had occurred. Further quantities of gas were then injected as before, and the whole procedure was repeated three or four times.

*Observations Made and Discussion of Their Importance.*—The experiments are presented in tabulated form in table 3. The observations all tended to show that while suction applied to a duodenal tube in the stomach was highly efficient in decompressing the stomach alone, it was necessary to insert the tube through the pylorus into the duodenum to obtain satisfactory decompression of the small intestine. In other experiments on cats, not reported here, it could be demonstrated that while the pylorus is occasionally patent to the passage of gas, usually a pressure of from 10 to 15 cm. of water in the duodenum was necessary to force any gas into the stomach from the intestine. This presupposes, of course, that the pylorus is in a state of contraction. It is to be appreciated that in the normal animal there is a rhythmic relaxation of the pyloric sphincter, and this intermittent relaxation seems to be the explanation for the not infrequent decompression of the small intestine which has been observed clinically in patients when the tip of the duodenal tube has remained in the stomach. The fact, however, that it was necessary to insert the duodenal tube into the duodenum in order to insure satisfactory decompression of the artificially distended small intestine of the cat is also borne out by clinical experience. Numbers of cases have been seen in which it has required from twelve to thirty-six hours to pass the duodenal tube through the pylorus with little or no decompression occurring during this period. On the other hand, when the duodenal tube at last passed beyond the pylorus a more or less constant aspiration of gas occurred with a concomitant decrease in the distention.<sup>17</sup>

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17. Wangenstein, O. H.: Therapeutic Considerations in Management of Acute Intestinal Obstruction: Technic of Enterostomy and Further Account of Decompression by Employment of Suction Siphonage by Nasal Catheter, Arch.

(Footnote continued on next page)

The intestine being an elastic tube, distention occurring in one segment tends with the passage of time to be more or less evenly distributed until all portions of the tube partake of it in a like degree. This fact was observed in the experiments on the seven cats. The equalization

TABLE 3.—*Observations on the Physiologic Mechanism of Decompression with Nasal Catheter Suction-Siphonage of the Small Intestine of Cats*

Cat	Length of Intestine, Cm.	Distance Below Pylorus at Which Air Was Injected, Cm.	Total Air Injected, Cc.	Degree of Negative Pressure Used, Cm. of Water	Quantity of Gas Recovered and Time Required with End of Duodenal Tube in		Comment
					Stomach	Duodenum	
1	50	17	80	150	0 cc. 1.5 hr.	10 cc. 1 hr.	40 cc. of air distended 20 cm. of small intestine; after 1½ hr. the distention was more evenly distributed; 80 cc. of air distended most of the small intestine; after 1 hr. the duodenum was collapsed
2	70	23	100	150	25 cc. 2.5 hr.	5 cc. 2 hr.	100 cc. of air distended the upper two thirds of the small intestine and some air passed into the stomach
3	85	28	125	115	35 cc. 3 hr.	30 cc. 2 hr.	50 cc. of air distended 40 cm. of small intestine; 100 cc. of air distended the whole small intestine and forced some air into stomach and cecum; at the end of 5 hr. most of gas in the bowel had disappeared although only one half of it had been recovered with suction
4	120	45	125	150	....	35 cc. 2 hr.	100 cc. air distended entire small intestine and some air passed into stomach and cecum; after 2 hr. the small intestine was still evenly distended except for 10 cm. of duodenum adjacent to the tip of the duodenal tube
5	120	50	130	150	....	40 cc. 2 hr.	Entire small bowel was distended; when suction was applied 10 cm. of duodenum became collapsed immediately; after 2 hr., 30 cm. of small intestine below the duodenal tube was collapsed; the remainder of the small intestine was evenly distended; peristalsis was fairly active
6	120	75	130	150	....	115 cc. 4 hr.	Peristalsis was quite active; at the end of 4 hr. only a small part of terminal ileum remained distended; increments of gas were seen continually passing up into the collapsed duodenum
7	130	125	100	115	....	65 cc. 1.5 hr.	Peristalsis was active; after 1 hr. the small intestine was much less distended than before; small quantities of gas were constantly being pushed up around the duodenal tube

Surg. 26:933-961 (June) 1933; The Management of Acute Intestinal Obstruction with Special Mention of the Character of the Vomiting and Distention, *Journal-Lancet* 54:640-645, 1934. Wangenstein, O. H., and Paine, J. R.: Treatment of Acute Intestinal Obstruction by Suction with Duodenal Tube, *J. A. M. A.* 101:1532-1539 (Nov. 11) 1933.

of pressure was far from perfect, but the tendency was present just the same, and the degree with which it occurred varied with the degree of peristalsis present in the bowel.

In a distended elastic and easily collapsible tube the application of suction to one portion of it immediately and completely evacuates and collapses that portion of the tube which is immediately adjacent to the point of negative pressure. If suction is applied to a distended elastic tube, the walls of which are not easily collapsible, the decompression will be complete throughout its length, provided kinks do not occur which occlude the lumen. The small intestine of both man and animals is both elastic and collapsible. When suction is applied to one portion of it the wall is immediately collapsed down around the point of negative pressure, and in the cat these collapsed portions of intestine measured from 6 to 10 cm. With the collapse of the walls the force of the suction sucked the mucosa tightly into the openings of the tube, holding it there with a force dependent on the degree of negative pressure used. This having occurred, no further decompression took place until with the passage of time gas slowly passed up from the portion of the intestine left distended and filled the collapsed portion. Under these circumstances if the duodenal tube or the adhering wall of intestine were slightly moved either by the movements of the intestine itself or by manipulation, decompression of the segment occurred again.

It is probably true that the foregoing mechanism is really the manner in which nasal catheter suction-siphonage effectually decompresses the distended intestine. In the two cats in which intestinal peristalsis was most active during the period of observation the best decompression was obtained. In these animals the sequence of events outlined occurred repeatedly, peristalsis slowly refilling the collapsed portion of intestine from the gas in the portion still distended. Such a theory of decompression seems to give the best explanation for the rather poor results not infrequently obtained in attempts to decompress an established distention due to paralytic ileus and the more rapid and complete decompression experienced in certain cases of mechanical obstruction in which peristalsis is hyperactive.

*Optimal Negative Pressure.*—The sucking of the wall of the bowel against the openings of the duodenal tube brings up two important questions. These are: 1. Will necrosis of the wall of the bowel occur at the points where the mucosa tends to be herniated into the openings of the duodenal tube? 2. Will milder degrees of negative pressure be more effective in attempts at decompression?

During the past four years at the University Hospitals necrosis of the wall of the bowel or of the mucosa was not observed at autopsy on thirty experimental animals that had been subjected to nasal catheter



suction-siphonage or on patients who had been treated by this method. Until further experimental work has been done, the second question cannot be satisfactorily answered. The limits of negative pressure with which decompression may be accomplished are probably fairly wide. The degree of suction that the siphon apparatus which we employ furnishes has proved satisfactory in clinical use. Negative pressure two and three times as high as that usually employed was not suitable because it collapsed the rubber tubing as well as the duodenal tube. A negative pressure approximately half that usually used has been tried on a fair number of patients and on eight or ten animals. The results have not been strikingly different from those obtained with stronger suction. One disadvantage of the milder degrees of negative pressure seems to be that mucus and the less fluid portions of the intestinal contents may more easily occlude the relatively small lumen of the duodenal tube. One gets the impression that the usual full strength suction is within the range of optimal values.

FACTORS MILITATING AGAINST DECOMPRESSION OF THE DISTENDED  
SMALL INTESTINE BY NASAL CATHETER  
SUCTION-SIPHONAGE

The observations made on the behavior of gas and fluid in rigid tubes have indicated several things which have a direct bearing on the decompression of the distended gastro-intestinal tract. It is well known that the intimate admixture of gas and fluid which is found in the normal intestine is not present in cases of stasis when distention occurs. Instead, the gas and water separate out, although the relative quantity of each present may vary greatly. Segments of the intestine became alternately filled with gas and fluid. The conditions studied in the vertical glass loops are thus reproduced to a certain extent. Suction applied to such an intestine, disregarding for the present the effect of kinks, elasticity and collapsibility of the wall of the bowel, must overcome the factor presented by the columns of fluid present in those loops which happen to be vertical. The presence of fluid in horizontal loops would have no effect except for the kinking and compression of underlying loops which it might cause owing to its weight. It was demonstrated in the measurements made on the glass tube with loops in all three planes how the pressure at different points of the system could be varied practically at will by changing the position of the apparatus as a whole and how the pressure was equalized throughout the system when the apparatus was so turned that all the fluid occupied horizontal loops. If it were possible to visualize perfectly the contained fluid in the intestine as it lies in the abdominal cavity, an approximation of this effect might be achieved by repeatedly turning the body in various direc-

tions. The positions of four dogs and several patients were changed repeatedly but with little or no improvement over results obtained without such maneuvers.

The presence of kinks in the bowel must be an important factor decreasing the efficiency of suction used for the purposes of decompression. Such kinks when formed or maintained by the weight of overlying loops must be real blocks to the equalization of hydrostatic pressure along the lumen of the bowel. This paper contains no experimental work on that point.

The collapsibility of the intestinal wall is a factor which has consistently entered into most of the experimental work discussed. It has always occurred immediately adjacent to the point of suction as soon as the fluid and gas contained in that portion of the bowel have been removed, and it has temporarily at least caused the process of decompression to cease until manipulation, peristalsis or the equalization of pressure due to elasticity partly redistends the collapsed portion. If it were not for the fact that even a mild degree of negative pressure produces this collapse, it might be possible to decompress a distended intestine rapidly by employing a fairly high degree of suction which would immediately overcome the other factors such as vertical columns of water and kinks in the bowel. However, I see no purpose to be served by using a greater negative pressure than suffices to remove gently the accumulations of gas and fluid which occur in the segment of the intestine immediately adjacent to the point of suction. As stated previously, the degree of negative pressure used clinically for decompression at the University Hospitals is probably within the range of optimal values.

#### PROBABLE PHYSIOLOGIC MECHANISM OF DECOMPRESSION

It will be worth while to try to integrate all the preceding observations and to describe the probable sequence of events which occurs when a distended small intestine is decompressed by suction applied to a duodenal tube. When the tube, perforated at intervals for about 9 inches (23 cm.) proximal to its tip, enters the stomach, this organ will be immediately and almost entirely emptied of both fluid and gas. The tube itself will then lie between the collapsed walls of the stomach. Should the tube be inserted no further along the gastro-intestinal tract, decompression of the bowel may or may not take place, depending principally on the tone of the pyloric sphincter and the strength of intestinal peristalsis. With the duodenal tube in the stomach, any gas it succeeds in removing from the small intestine must be brought to it by regurgitation from the duodenum. Such a tube, however, will be quite efficient in preventing an existing distention of the small intestine from increas-

ing or in preventing such a distention from occurring. Hibbard,<sup>18</sup> as well as McIver,<sup>19</sup> have shown by qualitative and quantitative analyses of intestinal gases that swallowed air is responsible for approximately 70 to 75 per cent of the gas present in the obstructed bowel. As the duodenal tube is gradually inserted further, it will finally pass through the pylorus and enter the duodenum, being propelled chiefly by gastric peristalsis but partly by its weight, if the patient be made to lie on his right side. During this period of transit, small quantities of both fluid and gas may be regurgitated through the pylorus. These will be immediately evacuated when they reach the vicinity of the tube. As soon as the duodenal tube has entered the duodenum decompression of this portion of the intestine proceeds rapidly until the walls of the intestine lie collapsed around the tube and held to it by the force of the suction. Since the perforations in the duodenal tube extend about 9 inches proximal to its tip, suction is maintained simultaneously in both the duodenum and the stomach. This effectively prevents any air swallowed from causing gastric dilatation. Concomitant with the decompression of the duodenum a decrease in the intraluminary pressure of the intestine occurs throughout its entire length. The decrease becomes less as the terminal ileum is approached. Columns of water are set up which, with the kinks in the bowel, tend to equalize the force of the suction. Movements of the patient and the peristalsis of the intestine as well as the elasticity of the wall of the bowel cause increments of both gas and fluid to pass up into the collapsed portion from the still distended more distal portions. These quantities of gas and fluid which finally reach the vicinity of the duodenal tube are evacuated when some movement of the patient or of his intestine momentarily dislodges the adherent wall of the bowel from the perforations in the duodenal tube. In this manner, with the passage of time, the process proceeds slowly until the entire small intestine has been decompressed.

DECOMPRESSION OF THE DISTENDED COLON BY MEANS OF  
SUCTION APPLIED TO INLYING RECTAL TUBES<sup>20</sup>

Soon after the first clinical use of nasal catheter suction-siphonage it was appreciated that a preexisting distention of the colon was affected

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18. Hibbard, J. S.: Gaseous Distention Associated with Mechanical Obstruction of the Intestine, *Arch. Surg.* **33**:146-167 (July) 1936.

19. McIver, M. A.; Benedict, E. B., and Cline, J. W.: Postoperative Gaseous Distention of the Intestine, *Arch. Surg.* **13**:588-604 (Oct.) 1926.

20. When colostomy has been performed for purposes of decompression in patients with obstruction of the large bowel the colon is often opened just enough to allow a rectal tube to be inserted into the lumen of the bowel. The application of suction to such tubes has seemed to aid decompression of the distended segment

little or none by its use. Sperling<sup>21</sup> has shown that the ileocecal valve is patent in the vast majority of patients to the retrograde passage of fluid or gas except under much higher pressure than physiologically occurs. This being true, suction applied to a nasal catheter inserted into the stomach or duodenum can affect a distention of the colon only by preventing the passage of swallowed air through the small intestine and into the already distended colon. Therefore, while suction applied to a nasal tube may not decrease a preexisting distention of the large bowel, it is of distinct benefit in decreasing the increase of such a distention.

The use of continuous suction applied to an inlying rectal tube as an aid in the control of colonic distention has been tried by various men with varying results. Pratt,<sup>22</sup> of New York, has been the most enthusiastic of these. In our own experience the procedure has not been very successful. On purely mechanical grounds its use would appear to be limited to cases of paralytic (inhibitive) ileus or obstruction of the colon on a neurogenic (spastic) basis in which no true mechanical obstruction existed.

*Difficulties to Be Overcome in Decompression of the Colon.*—In whatever type of obstruction of the large bowel it is used, negative pressure applied to an inlying rectal tube must overcome certain inherent difficulties before satisfactory results can be expected. The factors which most strongly militate against successful decompression are: (1) the more or less solid character of the content of the lower part of the bowel and (2) the inability to pass a rectal tube above the sigmoid flexure of the colon. In a previous section of this paper the optimal negative pressure to be used in decompression with suction has been discussed. Such a discussion is particularly pertinent in any consideration of decompression of the colon.

*Efforts to Overcome the Difficulties.*—It is readily appreciated that the more solid content of the lower part of the bowel requires greater negative pressure to draw it off through a tube than the contents of the small bowel require. In our experience it has been found that even if

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and lessened the danger of infection which a more complete immediate opening of the colostomy might produce.

The application of suction to enterostomy tubes has been practiced as a routine in cases of obstruction of the small bowel in which duodenal suction has not been entirely successful in decompressing the distended loops. These cases have not been studied critically enough to say whether any advantage accrues from such a procedure, but it has permitted us to measure the amount of gas escaping through the enterostomy tube.

21. Sperling, L.: Rôle of the Ileocecal Sphincter in Cases of Obstruction of the Large Bowel, *Arch. Surg.* 32:22-49 (Jan.) 1936.

22. Pratt, G. H.: Intestinal Evacuation by Hydraulic Suction: Further Uses of Suction-Siphonage, *Am. J. Surg.* 23:148-156, 1933.

negative pressures of two or even three times that used for the small bowel is employed, feces lodge in the openings of the rectal tube and effectively prohibit all suction. In an effort to obviate this difficulty, periodic irrigations of the colon and the rectal tube have been used, but with no great improvement in the practicability of the method. The use of double recurrent rectal tubes suggested itself as a possible means of securing a sufficient dilution of the feces to enable them to be drawn off. A no. 36 French rectal tube with four or six perforations in the side wall for the efferent tube and a no. 14 French catheter for the afferent tube have been used. These tubes were taped together and inserted in the rectum as far as possible without kinking. Tap water was used for irrigation. Fairly satisfactory results were obtained as far as the feces were concerned, but little or no decompression occurred proximal to the sigmoid flexure.

The rectum and sigmoid flexure of the colon present the most tortuous path found in the gastro-intestinal tract. This fact enhances greatly the difficulty encountered in blindly passing a flexible tube along its lumen and prevents a negative pressure created in the rectum from being at all effectual in the descending colon. We have repeatedly attempted to insert a rectal tube up into the sigmoid flexure, guiding it with the forefinger inserted through the anus along the side of the tube. In only one case has it been possible to insert such a tube more than 5 or 6 inches (12 to 15 cm.) without having it become caught in one of the numerous folds of mucous membrane and kinked to such an extent that suction applied to the distal end exerted no effect whatever. In one case the tube was easily passed well up the descending colon to the neighborhood of the splenic flexure.

Attempts to pass tubes into the descending colon through a sigmoidoscope have also proved unavailing. A height of from 18 to 20 cm. from the anus can uniformly be reached, but we have not yet been able to perfect a technic which will allow the tube to pass the acutely angulated sigmoid flexure.

*Experiments Performed on Cadavers.*—In four cadavers with the abdomen widely open and the viscera, with the exception of the colon, removed an attempt was made to evolve a technic which would permit a satisfactory decompression of the distended large bowel. In three of these four cadavers the lower part of the bowel contained considerable amounts of feces. The distal half of the colon in the fourth cadaver was practically empty.

Repeated attempts to pass a rectal tube above the sigmoid flexure without intra-abdominal manipulation were all unsuccessful in each of the four cadavers. Invariably the presenting tip of the tube once past the valves of Houston followed up the curve of the sacrum and impinged on the wall of the sigmoid flexure. Attempts to pass it further with the colon collapsed or distended tended to produce a sacculation in the wall of the bowel. It is conceivable that energetic attempts to insert the tube farther might possibly produce a perforation, although this did not occur in any of the cadavers studied. No amount of manipulation of

the tube could make it take the sharp turn to the left necessary to reach the descending colon.

It had been previously suggested that while the passage of a rectal tube above the sigmoid flexure might be impossible in the usual case, such a procedure would be possible at the time of laparotomy when the advantages of intra-abdominal manipulation could be obtained. We found this to be invariably the case in the four cadavers studied.

The colons were distended, and attempts were made to decompress them by connecting a water siphon to an inlying rectal tube. When the rectal tube was below the sigmoid flexure, decompression stopped as soon as the rectum had been emptied, the S-shaped flexure forming an almost perfect valve and preventing transmission of the negative pressure. The feces present in three of the cadavers were also effective in stopping the suction action, but this difficulty could satisfactorily be overcome by repeated injections of water alternated with periods of aspiration. When the colon was enormously distended so that the sharp turns in the bowel at the sigmoid flexure were partially straightened out some decompression of the entire colon could be obtained, but not enough to seem to warrant the use of such procedures on patients.

Granted that the rectal tube could be inserted as far as the descending colon, it remained to see what degree of decompression could then be accomplished. In the cadavers studied we were able to obtain satisfactory decompression of the entire descending colon but only very imperfect decompression of those portions of the colon proximal to the splenic flexure. The repeated injection of water through the rectal tube followed by short periods of suction did not effect any greater degree of decompression.

#### SUMMARY

Alexander Monro II, of Edinburgh, in 1767 used tubes inserted through the esophagus to remove fluids and gases from the stomachs of cattle. Adolph Kussmaul in 1867 applied this method to human beings with success. The application of continuous suction to inlying duodenal tubes originated with Ward, of San Francisco, in 1925. In 1931 Wangensteen further developed this method of combating intestinal stasis and distention. He used it with marked success in selected cases of acute mechanical obstruction.

Positive and negative pressures transmitted through a system of connected vertical rigid tubes, partially filled with fluid, are decreased in their transmission owing to the formation of unequal columns of water.

If a glass tube partially filled with water is bent to form loops in all three planes of space, the hydrostatic pressure at each end of the tube may be altered by changing the relative position of the system as a whole.

The nasal catheter suction-siphonage apparatus used at the University Hospitals is a water siphon so modified as to produce a continuing negative pressure within an attached duodenal tube. The effectual negative pressure furnished by the apparatus depends on several factors, chief of which are the relative position of the bottles with respect to the distal end of the duodenal tube and the relative proportions of fluid and gas aspirated at any one time.

The suction apparatus may be modified to produce any range of negative pressure up to  $-1,000$  cm. of water. By the interpolation of a third bottle the variations in negative pressure due to alternate aspirations of fluid and gas may be diminished. The third bottle may also be used to catch the fluid aspirated so that it can be returned to the patient if desired.

The quantities of gas and fluid aspirated can be calculated from readings on calibrated scales attached to the bottles.

The creation of a negative pressure at one end of the distended small intestine of anesthetized dogs and of a distended human small intestine removed at autopsy caused the immediate complete decompression of that portion of the intestine adjacent to the source of negative pressure and caused partial decompression of the remaining portions of the bowel.

The establishment of a negative pressure at one end of the anesthetized dog's small intestine distended partly with air and partly with water produced a series of air traps and a gradient of pressure.

Decompression of the distended small intestine of anesthetized cats by suction applied to a duodenal tube was periodic. Better results were obtained when the tube was in the duodenum than when it was in the stomach. The most important factor favoring decompression appeared to be movements of the intestines, either peristaltic or otherwise.

The factors which militate against decompression of the distended small intestine by suction are: (1) the formation of vertical columns of fluid and air traps, (2) kinks in the bowel and (3) collapsibility of the intestinal wall.

Decompression of the distended colon by means of suction applied to inlying rectal tubes is a great deal less satisfactory than is decompression of the distended small intestine by means of suction applied to inlying duodenal tubes, owing to the more solid nature of the contents of the large bowel and to the tortuous course of the sigmoid flexure of the colon.

#### CONCLUSIONS

1. Decompression of the distended small intestine by means of suction applied to an inlying duodenal tube is a satisfactory method of relieving distention.

2. The success of this method depends on the maintenance of a continuous moderate degree of negative pressure within the duodenal tube.

3. The insertion of the duodenal tube beyond the pyloric sphincter and movements of the intestine facilitate the decompression.

4. Decompression of the distended colon by means of suction applied to an inlying rectal tube is unsatisfactory owing to the sharply angulated flexures of the colon and to the more solid content of the lower bowel.

# HERNIA INTO THE UMBILICAL CORD AND RELATED ANOMALIES

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BROOKLYN

Hernia into the umbilical cord, or true congenital umbilical hernia, as the condition is now termed, is a comparatively uncommon anomaly. It is said to occur once in every 5,000 or 6,000 new-born infants.<sup>1</sup> Like all anomalies of embryonal development, in no two cases does it present exactly the same anatomic picture or the same surgical problem, although in a general way the manifestations are always similar. Furthermore, the chance that any one surgeon will see or operate on any large number of patients with uncommon anomalies is unlikely. Hence, the surgical procedures are as varied as the anatomic peculiarities and as the operative technics. For these reasons I believe that the case to be described here merits recording. The comments on closely related anomalies are based almost entirely on case reports in the literature and are given in order to emphasize by comparison or contrast the close relationship which exists. The drawings which I have copied illustrate this same point. The classification which I shall give will, I hope, bring under one heading several conditions that are undeniably closely related but which now appear in various classifications.

## EMBRYOLOGY

In order to understand the occurrence of so-called hernia into the umbilical cord and other closely related anomalies, it is essential to have a clear understanding of some of the anatomic structures of the human embryo and their connection with the umbilicus and gastro-intestinal tract.

In a recent article Truesdale<sup>2</sup> has given a brief but clear description of some of the embryology concerned here, and I have taken the liberty of copying it. In the 5 mm. embryo the digestive tract consists of a tube which is closed at both ends and attached to the dorsal part of the mesentery, which extends from one end of the embryo to the other. By the time the embryo is 9 or 10 mm. in length the liver has grown so large that it diminishes the available abdominal space, and the

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1. Milch, Henry: Adherent Congenital Umbilical Hernia, *Am. J. Dis. Child.* 42:608 (Sept.) 1931.

2. Truesdale, P. E.: Retroposition of the Transverse Colon, *J. A. M. A.* 104:1697 (May 11) 1935.



intestinal loop is extruded into the root of the celom of the umbilical cord (exocelom, or extra-embryonic celom), forming a physiologic hernia (fig. 1). At this stage, when the embryo is from 5 to 10 weeks old, the first rotation of the intestine takes place. While the intestine lies extra-abdominally (in the exocelom), the caudal limb lies to the left of the cephalic limb, and the small intestine assumes a position below and to the left of the colon. The colon assumes an inverted U shape and lies opposite the midline of the posterior abdominal wall.<sup>3</sup>

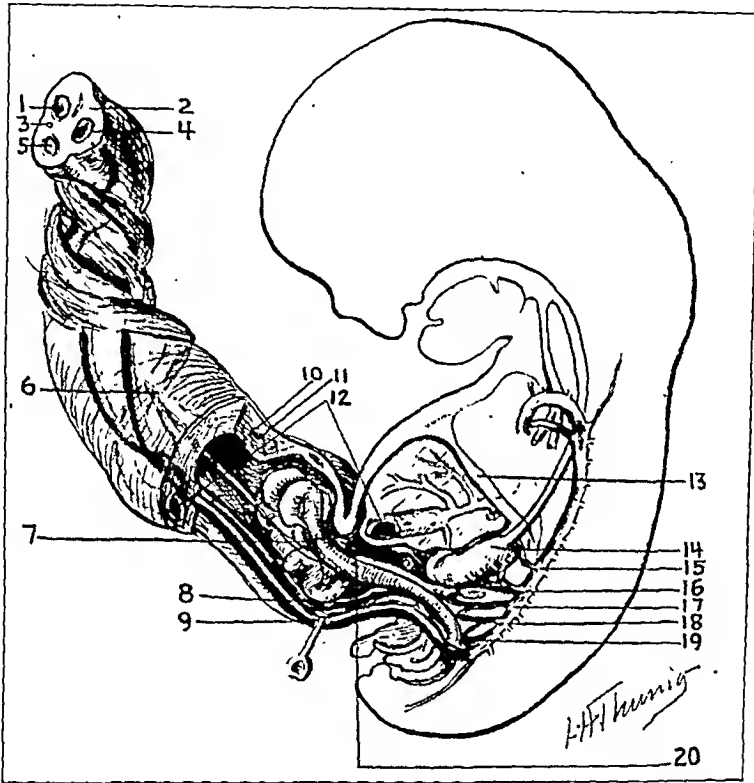


Fig. 1.—Human embryo, 23 mm. long. 1 and 5 indicate umbilical arteries; 2 and 10, omphalomesenteric vessels; 3 and 8, allantois; 4, umbilical vein; 6, distal end of the exocelom; 7, colon; 9, left umbilical artery; 11, cystic spaces in the cord wall which denote beginning obliteration of the exocelom; 12, umbilical vein (portion removed); 13, diaphragm; 14, stomach; 15 to 18, phrenic, celiac, superior and inferior mesenteric arteries; 19, right umbilical artery; 20, point at which it is assumed that adhesions form in a so-called paraduodenal hernia. (Copied from the drawing by Max Brödel in T. S. Cullen's <sup>7</sup> textbook, page 11).

The second stage, which is the important time when the midgut loop is returned to the abdomen, occurs at the tenth week. The return

3. Bailey, F. R., and Miller, A. M.: Textbook of Embryology, ed. 4, New York, William Wood & Company, 1923, p. 305.

of the intestine to the abdominal cavity is due to a fall in the intra-abdominal pressure, which results from the increase of space within the abdomen; the extra-abdominal pressure pushes back the contents of the sac,<sup>4</sup> or, according to Broman,<sup>5</sup> the intestine is gradually sucked back into the abdominal cavity when the latter has grown sufficiently large. The intestine does not return *en masse*. The proximal limb returns first and occupies the lower part of the abdomen below the liver. Thus the small intestine passes to the left below the colon and mesenteric vessels. The colon retains its inverted U shape, but the upper limb of the U is pushed transversely by the small intestine below and the stomach and liver above. The cecum returns last. As this enterocolic loop reenters the abdominal cavity it undergoes torsion of 270 degrees counterclockwise about the axis of the superior mesenteric artery.<sup>6</sup>

The following facts are added, as they have an important bearing on the etiology of the anomalies to be discussed.

*Authoritative Embryologic Facts.*—1. The exocoelom reaches its maximum size in the 30 mm. fetus, and the greater part of the small intestine develops in it<sup>7</sup> (fig. 2).

2. The exocoelom is lined with peritoneum which is a continuation of the parietal peritoneum of the abdominal cavity (celom, or intra-embryonic celom<sup>8</sup>).

3. The omphalomesenteric duct, or vitelline duct, and its vessels are present in very early fetal life. They pass from a loop of small intestine through the exocoelom to the yolk sac<sup>7</sup> (figs. 1 and 2).

4. Generally speaking, the omphalomesenteric duct disappears when the embryo is between 4 and 12 mm. in length, but its vessels persist long after the duct has disappeared.<sup>7</sup>

5. The intestine enters the abdomen about the third month.<sup>7</sup>

6. The exocoelom disappears about the third month.<sup>7</sup>

7. The umbilical ring closes about the third month.<sup>7</sup>

8. The amnion is reflected along the cord and at the fetal end of the cord passes directly to the skin of the fetus. The point of transition

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4. Bardeen, C. R.: *Am. J. Anat.* **16**:427 (Sept. 14) 1914.

5. Broman, I.: *Normale und abnormale Entwicklung des Menschen*, Weisbaden, J. F. Bergmann, 1911, p. 380.

6. Dott, N. M.: *Brit. J. Surg.* **11**:251 (Oct.) 1923.

7. Cullen, T. S.: *Diseases of the Umbilicus*, Philadelphia, W. B. Saunders Company, 1916.

8. Keith, Arthur: *Human Embryology and Morphology*, ed. 4, London, Edward Arnold & Co., 1921.

occurs from 0.5 to 1 cm. out on the cord and ends in a ring-shaped swelling.<sup>9</sup>

9. The adhesions which the ascending colon forms just before or after birth as the cecum assumes its final position in the iliac fossa are subject to a great range of variations, and many peritoneal folds and recesses may be formed. The purpose of all of them is to give fixation of the viscera to the abdominal wall.<sup>8</sup>

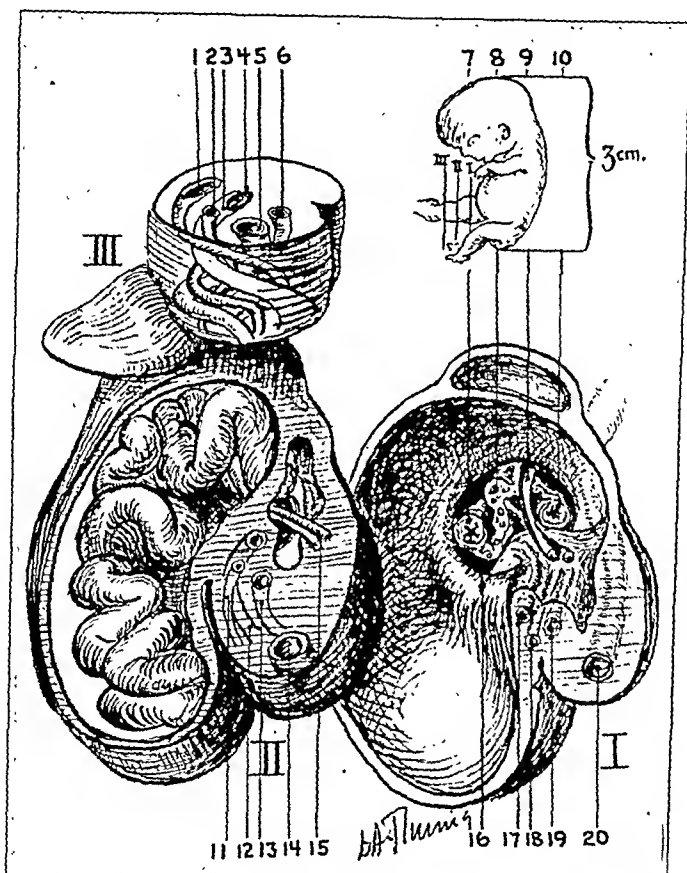


Fig. 2.—Human embryo, 3 cm. long, showing the structures of the umbilical cord. 1, 12 and 17 indicate right umbilical artery; 2, 11 and 18, allantois; 3, tip of exocoelom with omphalomesenteric vessels inside; 4, 15 and 9, omphalomesenteric vessels; 5, 14 and 20, umbilical vein; 6, 13 and 19, left umbilical artery; 7, small intestine; 8, mesentery of the small intestine; 10, large intestine; 16, umbilical ring at the base of the exocoelom. I, II and III indicate the level at which the sections were made, as shown in the sketch of the embryo in the upper right hand corner of the figures. (Copied from the drawing by Max Brödel in T. S. Cullen's <sup>7</sup> textbook.)

9. Runge, H. M.: Die Wundinfektionskrankheiten der Neugeborenen, in Die Krankheiten der ersten Lebensstage, Stuttgart, F. Enke, 1893. n. 56.

## REPORT OF A CASE

C. B. was born prematurely at the Prospect Heights Hospital at 10:20 a. m. on May 24, 1932, at eight and one-half months' gestation, by precipitate labor. He cried spontaneously. The weight was 3 pounds and 2 ounces (1,364 Gm.). The facies was mongoloid. I saw the infant immediately after birth, while the umbilical cord was still intact and the placenta undelivered.

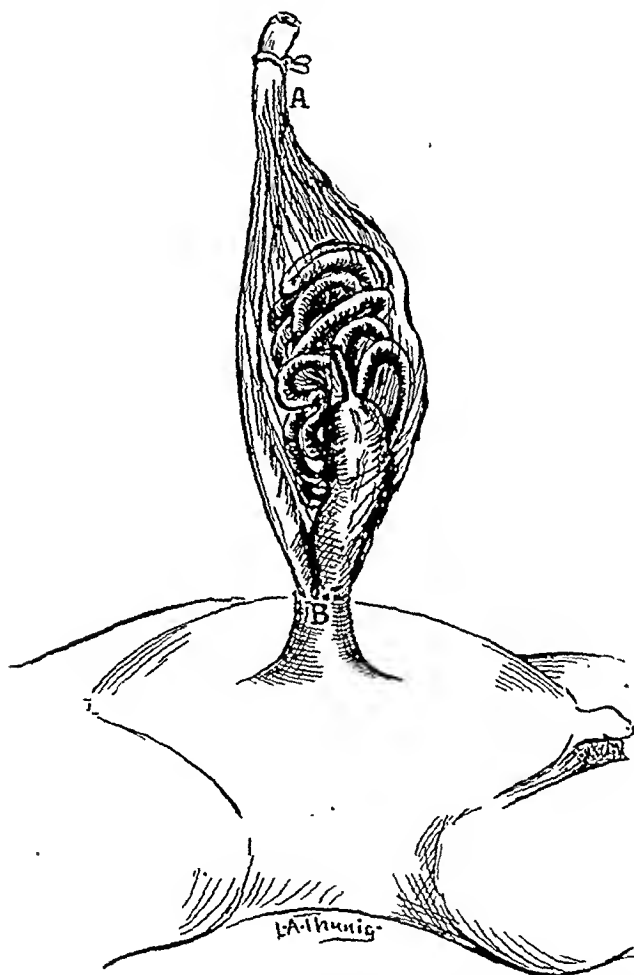


Fig. 3.—Appearance at birth of a so-called hernia into the umbilical cord as viewed from the right side. The sac was cut away, as described in step 2 of the operation, along the cord from *A* to *B*.

The umbilical area presented the usual elevated collar of skin with a typical thin but well defined crenated edge (fig. 3). This collar of skin extended from  $\frac{1}{2}$  to  $\frac{3}{4}$  inch (1.2 to 2 cm.) above the level of the abdomen and was not more than  $\frac{1}{2}$  inch (1.2 cm.) in diameter. A small but well defined umbilical cord occupied and was laterally attached to the upper angle of the collar of skin, and attached to the remainder of the circumference of the collar and going down into it was a thin, transparent membrane. From the collar this membrane spread outward on the cord to form a sac, which extended for about

3 inches (7.5 cm.) along the cord and was about 2 inches (5 cm.) in diameter. The cord did not present any twists and was practically straight from the collar to the distal end of the sac. At the neck of the sac, that is, at the collar of skin, the cord, though intimately attached to the sac, was sharply defined. The neck and base of the sac apparently consisted of amnion and peritoneum only. At the distal end of the sac the cord was not so well defined, and there was considerable fusing of the cord substance with the amnion and peritoneum. The vessels of the cord were not, however, spread out over the sac. The sac was not distended, in fact, it was extremely flaccid, nor was it completely filled, in spite of the fact that it contained the cecum with the appendix, a part of the ascending colon and what appeared to be the greater part of the small intestine. All these structures could be plainly seen through the wall of the sac. The cecum and ascending colon occupied the right and lower part of the sac, and the small intestine was to the left and reached a slightly higher level than the ascending colon and cecum. (Apparently the ascending colon had successfully rotated to the right of the small intestine, and that relationship did not change during operation.) I regret to state that I neglected to examine minutely that portion of the sac adjacent to the ascending colon to see whether any attempt at fixation had taken place, as might have been evidenced by the presence of adhesions or by the presence and location of the ileocolic vessels. Of course, it is possible that inspection might not have revealed the facts, as the parts were very small; the large intestine was about the size of a little finger, and the appendix was about  $\frac{1}{2}$  inch (1.3 cm.) long and less than  $\frac{1}{8}$  inch (0.4 cm.) in diameter. The diameter of the small intestine was about the same as that of cooked spaghetti. The intestine was not distended and was of good color.

Although I had some theoretical knowledge of the embryology of this anomaly, I had never before been confronted by the actuality. I decided to operate at once on the following grounds: 1. It was evident that the umbilical ring was very small, and it seemed probable that incarceration or strangulation might take place with the ingestion of food. 2. I believed that at least the distal part of the sac would dry up because of the large amount of cord substance present, just as the cord normally dries up, and that this would endanger life by rupture of the sac. (This opinion has been corroborated by the occurrence of such an event in at least two cases [Sanderson<sup>10</sup> and Carrington Williams<sup>11</sup>]). 3. It seemed impossible for the thin, fragile tissue of which the sac was composed to escape trauma or infection. (Peritonitis was present in one fatal case at the time of operation, two days after birth<sup>12</sup>).

*Operation.*—Operation was begun at 11 a. m. The cord had been tied a short distance above the distal attachment of the sac. No attempt had been made to reduce the intestinal hernia.

Step 1: An attempt was made to dissect the sac intact from the cord. This was obviously impossible, and the sac was entered at the distal end.

Step 2: The sac was then cut away from the cord by sharp dissection from the distal end to the collar of skin. No bleeding or vessels of the umbilical cord were encountered.

Step 3: The cecum and appendix presented themselves within the sac. The meso-appendix was well defined. A single ligature was placed around the appendix, and the meso-appendix and appendix were removed. The parts of the intestine maintained their relationship within the sac, and no difficulty was experienced in

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10. Cullen,<sup>7</sup> p. 462.

11. Williams, Carrington: *S. Clin. North America* 10:805, 1930.

12. Williams, Carrington,<sup>11</sup> p. 808.

keeping them there. A very brief, unsuccessful attempt was made to return the intestine to the abdominal cavity. The umbilical ring admitted the tip of the little finger and was apparently patent.

Step 4: A circular incision was carried around the collar of skin about 1/16 inch (0.15 cm.) or less from and parallel to the thin crenated edge and carried down to the peritoneum of the neck of the sac.

Step 5: The peritoneum could then be stripped away easily and quickly from the inside of the collar. Separation was carried down by blunt dissection until the inside of the abdomen was reached extraperitoneally.

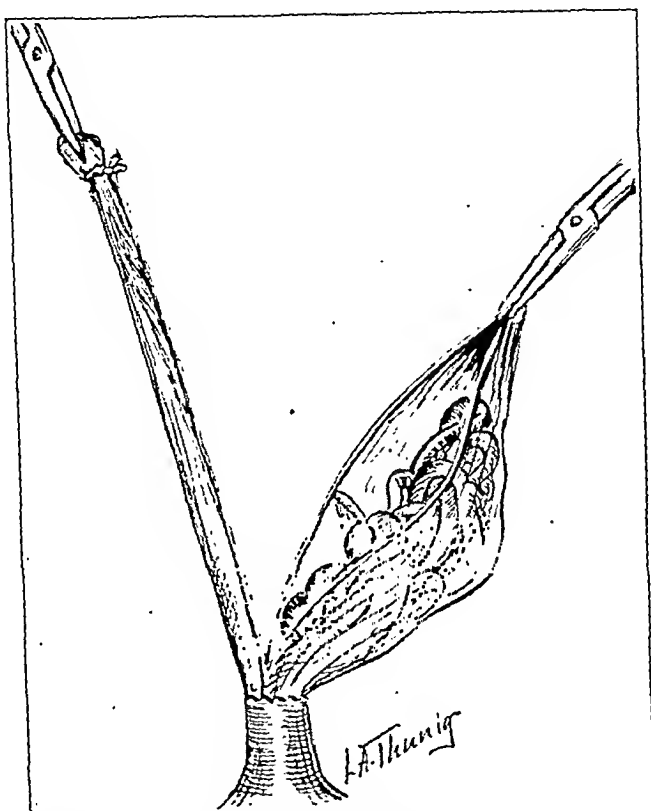


Fig. 4.—The appearance after the sac had been cut away from the cord at the conclusion of step 2. Step 3, removal of the appendix, was then carried out.

Step 6: Two incisions were then made, one above and one below the umbilicus. Each incision started at a median point on the cut edge of the collar; the collar was split, and the incision was carried along the median line of the abdomen for about 1 inch (2.5 cm.). The umbilical ring and the linea alba were split above and below the umbilicus down to the peritoneum. Still the intestine failed to return to the abdomen spontaneously, and it was left alone.

Step 7: The umbilical cord was then fixed by ligature and sutured to the cut edge of the linea alba above the site of the umbilical ring. The cord was cut so as to leave as short a stump as possible.

Step 8: The parietal peritoneum was separated by blunt dissection from the inside of the abdominal wall all around the opening, the immediate vicinity of the sutured stump of the umbilical cord being avoided. The base of the sac was then

spread out and was wide apart, with disappearance of the neck of the sac. The little ring of crenated skin had of course been severed when the umbilical cord was removed, and only a small remnant was left on the sac. The intestine still tended to remain within the sac, at least a considerable portion of it, particularly the large intestine.

Step 9: The opening of the sac was then closed with a continuous catgut suture, which was widely placed, with a good distance left between stitches. With the

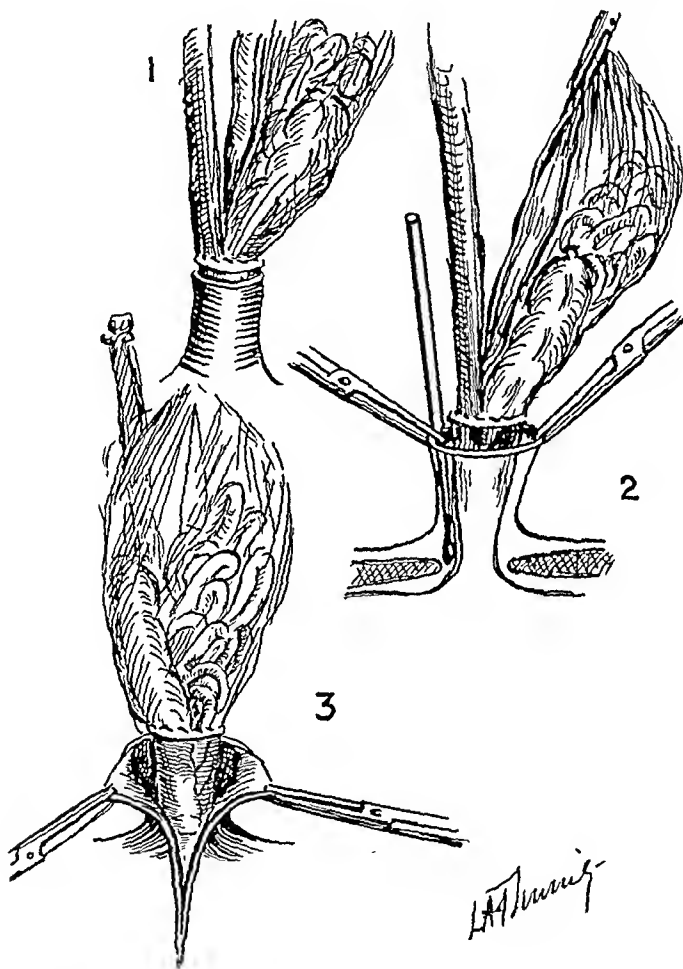


Fig. 5.—Operative steps 4, 5 and 6. Step 4 (at 1), circular incision around the collar of skin, as viewed from the right side. Step 5 (at 2), stripping the peritoneum away from the inside of the collar and carrying the separation into the abdominal cavity extraperitoneally. These views are from the right. Step 6 (at 3), the incision is made below the umbilicus through the collar and then in the midline of the abdomen for about 1 inch (2.5 cm.), carried down to the peritoneum, splitting the linea alba and the umbilical ring. Exactly the same procedure was carried out above the umbilicus. This view is taken from below.

tightening and tying of this suture the size of the sac diminished markedly, and the sac and intestine were literally dropped into the abdomen.

Step 10: Because of the thinness of the abdominal wall and the minuteness of the parts, I deemed it unwise either to attempt suturing it in layers or to bury

any catgut in the tissues. The abdomen was closed with through and through Lembert silkworm gut sutures (peritoneum excluded) with as much overlapping as possible without tension. A few fine silk sutures were used for the skin.

The operation was completed at 11:40 a. m. The anesthesia was negligible, as the child received only an occasional whiff of ether.

*Progress.*—The infant stood the operation well. No postoperative distention occurred, and the bowels moved spontaneously on the second day after operation.

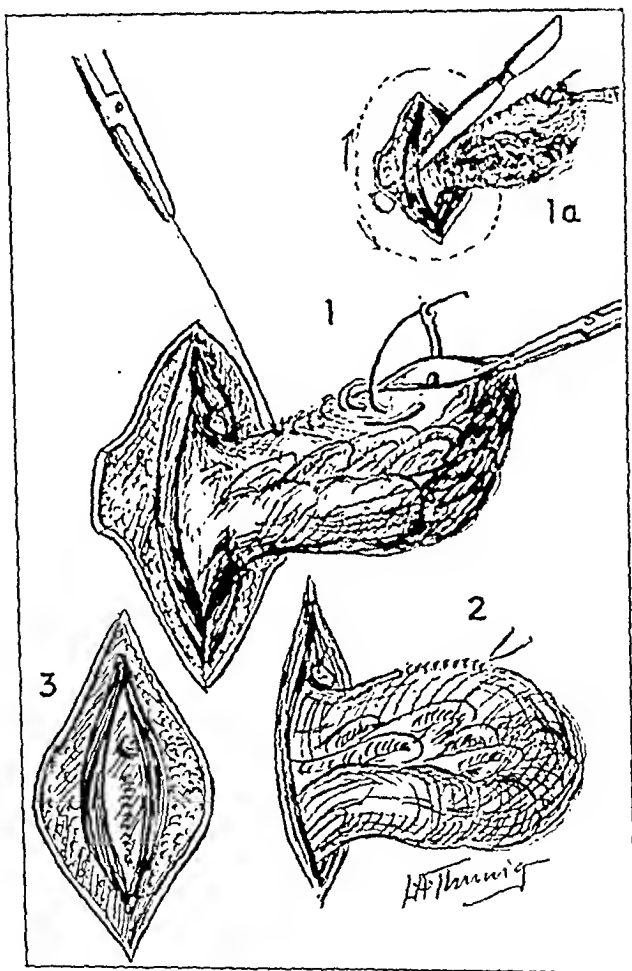


Fig. 6.—Operative steps 7, 8 and 9. 1, step 7 has been completed, and the stump of the umbilical cord is sutured to the split linea alba. Step 8 (1a): Separation of the peritoneum from the abdominal wall by blunt dissection has also been completed, and the opening in the sac is being sutured. Step 9 (at 2) shows the sac sutured, with a decrease in the size due to the pulling together of the widely placed continuous suture. 3, showing the appearance at the completion of step 9, with the sac and its contents returned into the abdomen.

He nursed well at breast and was given also a supplementary formula, as the breast milk was deficient. He vomited only once postoperatively. The wound remained clean, and the sutures were removed on the sixth day. Shortly afterward an irregular slough developed at the upper angle of the wound. It involved only



the skin and was removed. Wide separation of the edges of the skin was prevented with an adhesive plaster strapping. The small stump of cord, however, made its way through the sloughed area. On June 2 the wound was clean, and the cord stump had separated. The infant was discharged on June 3, ten days postoperatively.

The temperature reached 101 F. within the first twenty-four hours after operation. Thereafter it did not rise above 100 F.

At birth the infant weighed 3 pounds and 2 ounces (1,364 Gm.). After a slight initial loss he gained progressively, and when 10 days old he weighed 4 pounds and 4 ounces (1,928 Gm.).

The nurses' report shows that in addition to one vomiting spell there was occasional regurgitation; otherwise the course was uneventful.

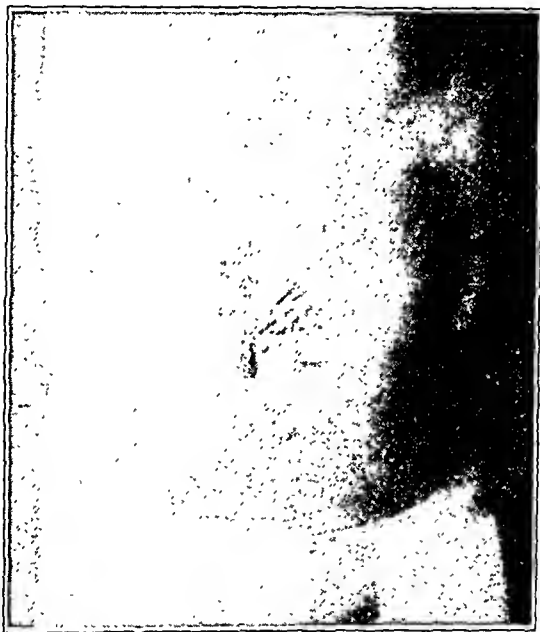


Fig. 7.—Photograph of abdomen of C. B., taken on July 8, 1935.

The child was seen by me after he was discharged from the hospital. The wound healed without difficulty, and the weight increased slowly. For several months after operation there appeared to be some weak, thin spots about the wound, without herniation. At 6 months there still remained one weak spot. In June 1935 the weak spots had disappeared, and there was no evidence of hernia. The abdominal wall was firm and presented the appearance shown in the photograph (fig. 7).

*Roentgen Examination.*—Being interested to know what influence the anomaly and/or its operative treatment might have on intestinal rotation, I had roentgenograms made.<sup>13</sup> The report, made by Dr. Charles J. Search, was as follows:

"On July 8, 1935, roentgenograms were made of the boy, aged 3 years and 2 months. They were made after the ingestion of a barium sulfate meal, together

13. It is an interesting sidelight to note the psychologic reactions of the parents of this infant toward a roentgen examination and also to note to what

with the giving of a barium sulfate enema, in order to show the size, shape and position of the stomach and large intestine. The plates show that the cecum is in the right iliac fossa, the ascending colon lies on the right side and the hepatic flexure is present. The transverse colon turns to the left on a level with the greater curvature of the stomach but, instead of rising to form the high splenic flexure, drops directly downward. At about the same level as the cecum on the right the transverse colon is reflected upward and, extending diagonally across the abdomen, forms what would normally be a splenic flexure but is really another hepatic flexure, which lies directly above the normal hepatic flexure. From this second hepatic flexure the descending colon arises and, following the course of the ascending loop of the transverse colon, passes diagonally downward and across the abdomen to the rectum and anus. The position of the different organs in the abdominal cavity as marked on the roentgenograms were carefully checked before and after the taking of the roentgenograms. The diagnosis is incomplete rotation of the transverse and descending colon."

*Comment.*—This report shows that the spreading out of the transverse colon across the upper part of the abdomen, with the formation of a splenic flexure and descending colon on the left, was incomplete. According to the best authorities this spreading out of the transverse colon is produced by the pressure of the small intestine from below and by the pressure of the stomach and liver from above. Thus, with the major part of the small intestine confined in the exocoelom outside of the abdomen until after birth and in view of the fact that some visceral fixation had probably taken place by that time, one can readily understand the *modus operandi* in this case. This brings up the question of what bearing intestinal rotation and the behavior of the exocoelom may have on one another. This is a lengthy topic, and I may say here only that in this case there was a definite relationship and the persistent extra-abdominal exocoelom was the cause of the failure of the rotation. That this relationship also exists in cases of so-called paraduodenal hernia, which will be discussed later in this paper, has been definitely shown by Papez.<sup>14</sup> Whether faulty rotation is always due to the faulty behavior of the exocoelom or vice versa or whether the actuating factor is variable is a question that is still unanswered.

In spite of this infant's early surgical experience and his present intestinal anomaly, he has been practically free from gastro-intestinal disturbances. He did not walk until he was 2½ years old, and he really does not talk as yet (July 1935).

extent one's enthusiasm and interest may influence one's actions. I sent the infant's father a letter explaining that I wished to have a roentgenogram made to determine the position of the intestine and volunteering to pay for it, as the family were in moderate circumstances. I fully expected an appreciative reply; instead I was notified that the child was well and did not need a roentgen examination; furthermore, the parents refused to have it made. In a spirit of foiled enthusiasm and resentment I drove rapidly to the home and found the mother, the infant and an older son. After much arguing and explaining I hustled the entire family into my car, rushed them to Dr. Search's office and obtained the roentgenogram. This explains why the barium was given by mouth and by rectum at the same time. It was an only opportunity and had to be seized. While the roentgenograms were being taken I learned that the parents believed that I was having the plates made so as to find some reason to operate again. Will the public ever learn that the physician sometimes thinks of something other than dollars and cents?

14. Papez, J. W.: A Rare Intestinal Anomaly of Embryonic Origin, *Anat. Rec.* 54:197, 1932.

There is a hydrocele of the cord, which shows well in the photograph, and the mongolian type of facies that was noticeable at birth is now very marked and associated with imbecility or idiocy.

*Criticism of the Operation Based on Embryologic Considerations, Operative Observations and Results.*—Step 1: No comment is necessary.

Step 2: The lateral opening simplified the handling of the cord and the contents of the sac.

Step 3: The removal of the appendix was not justified, but the temptation was great and the risk seemed negligible in view of the simplicity of the procedure and the sterility of the gastro-intestinal tract. The fact that no difficulty was

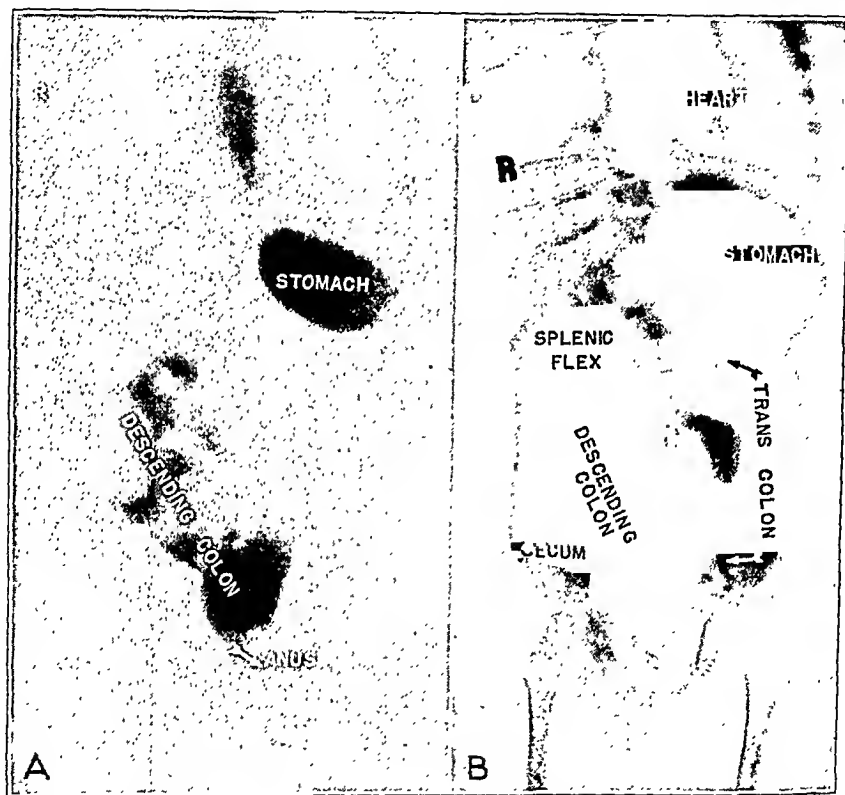


Fig. 8.—Roentgenograms of C. B., taken on July 8, 1935. A small amount of barium was given by mouth and by rectum to determine the intestinal capacity. *A*, the position of the descending colon and the beginning of transverse colon are well shown and make the interpretation of *B* much simpler. *B*, a roentgenogram taken immediately after the film shown in *B* (see text).

experienced in keeping the intestine within the sac, the failure of reduction within a patent umbilical ring and the maintenance of the intestinal relationship may have been due to any of four conditions: (1) a persistent omphalomesenteric duct, which is given as a cause for failure of reduction in at least three cases;<sup>15</sup> (2)

15. (a) Sheen, W.: *Bristol Med.-Chir. J.* 19:310, 1901. (b) Fraser, John: *Surgery of Childhood*, Baltimore, William Wood & Company, 1926, pp. 774 and 776. Williams.<sup>11</sup>

possible attempt at fixation of the ascending colon to the base and neck of the sac; (3) an umbilical ring that was too small, and (4) simple adhesions. Frankly, I did not look for the omphalomesenteric duct, nor did I discover it by chance. I presume that showed negligence; but I was impressed with the fact that the ascending colon was the offending factor, and I still believe that it was. It has been shown that the lining of the exocoelom is peritoneum which is continuous with the parietal peritoneum of the abdomen and that this exocoelomic peritoneal sac may return to the general abdominal cavity during embryonic life.<sup>16</sup> It is only a fair assumption to believe that under normal conditions this exocoelomic sac would spread out and become parietal peritoneum of the abdomen. Taking this probability into consideration with the fact concerning adhesions of the ascending colon, as given in this paper under the heading "Authoritative Embryonic Facts," makes me feel fairly certain that in this case there was some attempt at fixation of the cecum. At the time of operation I felt so certain that that had taken place and that the blood supply to the colon was involved in the base and neck of the sac that I believed the handling of the sac as any ordinary hernial sac might be handled would result in interference with the colonic blood supply and therefore concluded that it was imperative to reduce the sac, or part of it, with the intestine. This accounts for the technic used in the remainder of the operation.

That a too small umbilical ring was not the essential cause for failure of reduction is shown by the following steps: Simple adhesions may have been present.

Steps 4 and 5: This seemed to be the easiest way of establishing the identity of the peritoneum. The peritoneum stripped easily. There was also a direct approach to the umbilical ring.

Step 6: The failure of reduction with the ring split confirmed the opinion regarding fixation of the colon. This, of course, does not account for the failure of the small intestine to reduce, and it is possible that there was a persistent omphalomesenteric duct present which I overlooked or, possibly, simple adhesions, which are mentioned in one of the cases reported.<sup>15a</sup> I must say that my attempts at reduction were feeble, for I felt that handling or traumatizing the intestine was the one thing that should be avoided. I believe that the following out of this dictum was the most important factor in the uneventful recovery. In one case that has been reported in which reduction was difficult the child died of peritonitis three days after operation.<sup>17</sup> In Hope's case the small intestine was adherent to the sac but was easily separated. What the operators said they believed to be the appendix was intimately fused with the tissue of the cord and had to be ligated and cut off. Sheen<sup>15a</sup> gave as his opinion that it was a remnant of the omphalomesenteric duct.

Step 7: The cord was removed deeply with the idea of lessening the possibility of the development of an incisional hernia. The progress shows that the cord either should have been more radically removed or should have been disregarded, tied off in the usual manner after separation from the sac and allowed to take care of itself, as the stump actually did. Just how the cord was handled is not mentioned in many of the case reports. With cutting of the cord the small ring of crenated skin also was of necessity cut, and the small amount remaining on the sac was left in situ.

Step 8: This procedure was performed with the idea of widening the base of the sac, eliminating the neck of the sac and making the reduction of the sac

16. Mall, F. P.: *Arch. f. Anat. u. Physiol., supp.*, 1897, p. 403. Jackson, C. M.: *Anat. Rec.* 3:361 and 396, 1909. Papez.<sup>14</sup>

17. Powers, D'Arcy: *Tr. Path. Soc. London* 39:108, 1888.

and intestine easy of accomplishment and without any constriction about the intestine. It successfully fulfilled all three requirements. The fact that even then the intestine did not slide into the abdomen strengthened the idea of intestinal fixation, already discussed.

Step 9: This step accomplished closure of the sac with a marked diminution in the size, thus again aiding the reduction *en masse*.

Step 10: This appeared to be the quickest, safest and easiest procedure by which to close the abdomen. The ultimate results justified it. Had it been realized at the outset that reduction of the contents of the sac independent of the sac was to prove unsuccessful, then it would have been much better surgery to have commenced with step 4, followed by 5, 6, 2, 3, 7, 8, 9 and 10, in the order given.

#### COMMENT

It is generally agreed that operation for so-called hernia into the umbilical cord and amniotic hernia, which is to be described later, gives the best results if operation is performed soon after birth. The ability of the new-born to stand a major surgical procedure has been commented on by many. Freshman<sup>18</sup> confirmed these opinions and reported that in his case (in which there was a large amniotic hernia), operation was performed two hours after birth. He also stated that his search of the literature revealed the report of only one case in which operation was performed so soon after birth. McCaughan<sup>19</sup> reported a case of massive amniotic hernia in which operation was performed soon after birth, the appendix was removed and recovery followed. He, however, stated no definite time, and only meager details of the case are given. Reed<sup>20</sup> reported a case in which rupture of the sac and evisceration occurred under most unsanitary conditions. The infant was operated on two hours after birth; the appendix was removed, and recovery followed. Hernia into the umbilical cord does not seem to occur as commonly as amniotic hernia. Cases have been reported by Williams,<sup>11</sup> Fraser,<sup>15b</sup> Powers<sup>17</sup> and Sheen<sup>15a</sup>. Haines and McIlroy<sup>21</sup> have reported an interesting case of amniotic hernia.

#### CLASSIFICATION AND NOMENCLATURE OF SO-CALLED HERNIA INTO THE UMBILICAL CORD AND CLOSELY RELATED ANOMALIES

Even in excellent and authoritative textbooks little has been written concerning these conditions, and the classification varies. In "Nelson's Loose-Leaf Living Surgery" there are about ten lines; Kelley<sup>22</sup> in his book entitled "Surgical Diseases of Children" gave about one page;

18. Freshman, Edgar: *Lancet* **2:701** (Sept. 23) 1933.

19. McCaughan, J. J.: *Memphis M. J.* **10:17** (March) 1935.

20. Reed, E. N.: *Infant Disemboweled at Birth—Appendectomy Successful*, *J. A. M. A.* **61:199** (July 19) 1913.

21. Haines, C. E., and McIlroy, P. T.: *Am. J. Surg.* **21:297** (Aug.) 1933.

22. Kelley, S. W.: *Surgical Diseases of Children*, New York, E. B. Treat & Company, 1909, p. 939.

Fraser<sup>15b</sup> in his book, "Surgery of Childhood" and Cullen<sup>7</sup> in his book entitled "Diseases of the Umbilicus" gave considerably more. In an article written as late as 1907<sup>22a</sup> amniotic umbilicus is classified under tumors of the umbilicus. Williams,<sup>11</sup> following Cullen's classification, included under the heading of amniotic hernia a case of his own in which he stated there was no protrusion of the organs. Kelley classified them under the heading malformations of the linea alba and the umbilicus.<sup>22</sup> This was encouraging, but there the classification ended. Bearing these facts in mind I feel justified in suggesting a revised classification, even though it is only for the purpose of presenting the remainder of this paper in a systematic and anatomically orderly manner. I am fully aware that I am presuming greatly in this attempt at revision of the work done in many instances by masters, and it is with my humblest apologies that I offer my suggestions.

As a starting point I shall use Cullen's<sup>23</sup> classification. Under the heading of umbilical hernia Cullen gave the items in the following list but not in this order. For my convenience I have taken the liberty of changing his order as follows:

1. Umbilical hernia in the adult
2. Serous umbilical hernia
3. Cysts of the umbilicus
4. Small umbilical hernia at birth
5. Hernia into the umbilical cord
6. Congenital nipping off of a hernial protrusion
7. Amniotic hernia.

The first four of these groups can be excluded, as they do not represent anomalies and hence are not closely related to the present topic. The heading "cysts of the umbilicus" is not meant to include cystic conditions of the umbilicus associated with anomalies of the allantois or omphalomesenteric duct. These are, of course, true anomalies but belong to a classification apart from the one which I wish to emphasize, namely, anomalies dependent on the misbehavior of the exocoelom. This leaves three items which are closely related, as I shall later show, and to these three I wish to add three more which, though mentioned in the literature, are not definitely classified. Under the present nomenclature the list is now as follows:

- |   |                                   |
|---|-----------------------------------|
| 1. Hernia into the umbilical cord                 | } From Cullen's<br>classification |
| 2. Congenital nipping off of a hernial protrusion |                                   |
| 3. Amniotic hernia                                |                                   |
| 4. Amniotic umbilicus                             | } From the<br>literature          |
| 5. Amniotic linea alba                            |                                   |
| 6. Paraduodenal hernia, or retroperitoneal hernia |                                   |

22a. Gallant, A. E.: *Internat. Clin.* 1:151, 1907.

23. Cullen,<sup>7</sup> p. 459.

From an anatomic and embryologic etiologic standpoint these may be conveniently divided into four groups, as follows:

RELATED ANOMALIES OF THE UMBILICAL CORD, UMBILICUS,  
LINEA ALBA AND ABDOMINAL CONTENTS

- Group I. Persistent extra-abdominal exocelom
  - (a) With intestinal inclusion; patent umbilical ring (hernia into the umbilical cord)
  - (b) With cutting off of the intestinal loop; umbilical ring usually closed (congenital nipping off of a hernial protrusion)
- Group II. Persistent intra-abdominal exocelom with intestinal inclusion; return of the exocelom and intestine to the abdomen *en masse*
  - (a) Before rotation of the ascending colon: right-sided persistent intra-abdominal exocelom with intestinal inclusion (right-sided paraduodenal hernia)
  - (b) After rotation of the ascending colon; left-sided persistent intra-abdominal exocelom with intestinal inclusion (left-sided paraduodenal hernia)
- Group III. Amniotic replacement of the deficient umbilicus and linea alba without visceral protrusion
  - (a) Umbilical only—amniotic umbilicus (amniotic umbilicus)
  - (b) Umbilicus and linea alba—amniotic linea alba (indefinite nomenclature)
- Group IV. Amniotic replacement of a deficient linea alba with protrusion of the viscera into the hernia—amniotic hernia (amniotic hernia)

This list gives only six conditions, and I feel certain that there are others which are closely related to those that have been named. These will be briefly discussed. The case I have reported, in which there was incomplete rotation of the colon, tends to prove that there is at least some basis for suspecting that rotation of the intestine may be to some degree dependent on the time and the way the exocelom and its contents return to the abdominal cavity; or, if one prefers, the time and the way the exocelom and its contents return to the abdomen may be dependent on the rotation of the intestine. In the case reported it appears that the failure of rotation was due to the absence of the small intestine in the abdominal cavity. In the case of so-called paraduodenal hernia Papez<sup>14</sup> stated the opinion that the position, right or left, of the reduced exocelom depends on the time that the adhesions are formed with regard to the stage of rotation. Is it not quite as possible that the rotation or nonrotation of the intestine may depend on how and when the exocelom with its intestinal contents comes into the abdomen? I have mentioned these facts here to show that it is reasonable to believe that other anomalies will fall within the suggested classification. However, I shall confine my discussion to the six named.

In the following discussion I wish to give credit to those on whose work some of the nomenclature is based. Some of the arguments put forth hereafter have already been expressed, especially by Freshman.<sup>14</sup>

*Persistent Extra-Abdominal Exocoelom with Intestinal Inclusion (Hernia into the Umbilical Cord).*—Mészáros<sup>24</sup> gave the name coeloma funiculi umbilicalis persistens to this condition. Freshman stated definitely that the present name is inaccurate. It is true that in the early embryo the initial intestinal tube is pulled or pushed into the exocoelom, but that is a normal condition. The major portion of the small intestine actually grows in the exocoelom; it has never been in the abdominal cavity. Hence, if it fails to enter the abdomen as it should and remains outside in the exocoelom, I do not see how one can consider it a hernia in the strict sense of the term.

The case reported is an excellent example of so-called hernia into the umbilical cord, and the report brings out all the anatomic details. The relationship of the sac to the cord tissues and the amniotic cord covering may vary with the site of the exocoelom. Cullen showed beautifully with drawings from the fetus that the exocoelom may be centrally or laterally placed in the proximal end of the cord. Thus in one case the umbilical vessels were spread out over one side of the sac.<sup>15a</sup> A persistent omphalomesenteric duct has already been mentioned as a cause of failure of reduction, and consequently one must consider it an associated etiologic factor in the production of the anomaly. The same argument holds true regarding adhesions within the exocoelom or at the umbilical ring.

*Persistent Extra-Abdominal Exocoelom with Cutting Off of an Intestinal Loop (Congenital Nipping Off of a Hernial Protrusion).*—In this condition a loop of intestine of varying length may remain within the persistent extra-abdominal exocoelom and be cut off from the intestine within the abdomen by a closing or narrowing of the ring or by adhesions across the ring. In these cases the proximal and distal ends of the intestine that are usually adjacent to the amputated loop terminate in blind ends within the abdomen.<sup>25</sup> It is obvious that the exocoelom could not enter the abdomen and the intestine remain out.

When one considers the *modus operandi* involved in the production of what is called congenital nipping off of an umbilical hernial protrusion, one cannot help but wonder whether this same process is in some cases a factor in the production of congenital atresia or stenosis of the intestinal tract.

24. Mészáros, K.: Arch. f. klin. Chir. **158**:650, 1930.

25. Kern, T.: Ueber die Divertikel des Darmkanals, Inaug. Dissert., Tübingen, L. F. Fues, 1874.



In Ahlfeld's<sup>26</sup> case, described by Cullen,<sup>27</sup> the major part of the small intestine and a portion of the large intestine were outside of the abdomen and attached to the umbilicus by a thin pedicle. Is it not a fair assumption that there may have been some cases in which only the intra-abdominal defect was found and the real etiologic factor was missed, because of a complete separation from the body and loss of the amputated loop during delivery? Is it not a fair assumption also that in some cases the constriction of the intestine may not have reached the point of complete separation but had resulted only in atrophy with atresia or stenosis and then, owing to their decreased size, the intestinal loops may have entered the abdomen through the constricted umbilical ring? Certainly this does not seem improbable, particularly in that portion of the intestinal tract which normally occupies the exocoelom in embryonic life. The catching of several loops at one time or successively could readily account for the multiple and separated areas of atresia or stenosis so frequently noted in these cases. Atresia or stenosis in that portion of the intestinal tract which does not normally occupy the exocoelom, that is, the duodenum and hindgut, cannot be so readily explained. Yet how can one prove that the duodenum may not at times abnormally occupy also the exocoelom? In that event, in the presence of a constricting umbilical ring or adhesions it might undergo atresia, stenosis or even amputation. This appears not impossible when one considers the anatomic nearness of the duodenum to the embryonic exocoelom and umbilical ring. It is rather noteworthy that the hindgut, atresia or stenosis of which cannot readily be explained by this theory, is, according to J. Fraser,<sup>15b</sup> uncommonly the seat of errors.

In view of the fact that Ahlfeld reported the case previously mentioned in 1873, it is likely that other writers have entertained the same opinions that I have expressed or similar ones, and in all probability a thorough search of the literature would show this to be true. Nevertheless, I have been unable to find a textbook or article which indicates it. The nearest I discovered was in an article by Fritz Laessing,<sup>28</sup> who mentioned Ahlfeld, Strang and Nahrath as supporters of the theory that an abnormal pull of the omphalomesenteric duct on the intestine in the exocoelom is an important factor in the production of atresia and stenosis of the intestine. Laessing then ruled out their theory on the ground that the duodenum and part of the colon never occupy the exocoelom and that multiple atresias or stenoses could not be explained on that basis.

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26. Ahlfeld: *Arch. f. Gynäk.* 5:230, 1873.

27. Cullen,<sup>7</sup> p. 464.

28. Laessing, Fritz: *Arch. f. Kinderh.* 97:1, 1932.

I have already stated that to me it seems possible that the duodenum might under abnormal conditions occupy the exocoelom. Laessing,<sup>28</sup> in his discussion of intestinal atresia, etc., stated the belief that the duodenum or terminal part of the colon never occupies the exocoelom. Aeby<sup>29</sup> reported a case, with excellent photographs, and referred to four similar cases of a diverticulum of the heart in a child with so-called hernia into the umbilical cord. In this case the base of the hernia was about the size of a spectacle lens. The hernia contained small intestine and a pulsating mass, both of which were covered by the usual transparent membrane. The pulsating mass was about 1 cm. in diameter. The child lived three hours. Postmortem examination revealed that the pulsating mass was the end of a diverticulum of the heart and was connected with the heart proper by a pedicle of heart muscle about the thickness of a lead pencil. The heart occupied its normal place in the thoracic cavity and was, other than the diverticulum, normal. Although no definite bands were found, the author concluded that some must have existed some time in early fetal life.

Certainly if the development and behavior of the exocoelom are such as to allow, under abnormal conditions, a portion of the heart to enter the exocoelom and then to hold it there by means of adhesions or other factors with such force as to produce a diverticulum, as described in the case just mentioned, it seems only logical to believe that abnormally the duodenum, the later end of which normally occupies or is in close proximity with the exocoelom, and the hindgut, the continuity of which normally occupies the exocoelom, might both readily get into the exocoelom and, once in there, might under continued abnormal development be ensnared with resulting atresia, stenosis or amputation. It has been demonstrated in actual cases that intestinal loops normally in the exocoelom have been amputated. Then why not amputation of intestinal loops accidentally occupying the exocoelom? One thing is certain, and that is that the fact that the duodenum and hindgut do not normally occupy the exocoelom is not sufficient evidence in itself to prove that accidents of the exocoelom can be absolutely ruled out as an etiologic factor in intestinal atresias, stenoses and amputations including the duodenum and the hindgut.

Certainly there must be other etiologic factors in some cases of intestinal atresia and stenosis, but to me it seems not improbable that in some cases the anomaly is etiologically closely related to congenital nipping off of an umbilical hernial protrusion.

*Persistent Intra-Abdominal Exocoelom with Intestinal Inclusion.*—The following material is abstracted and quoted from a paper by James Papez entitled "A Rare Intestinal Anomaly of Embryonic Origin."<sup>14</sup>

29. Aeby, H. Koller: Arch. f. Gynäk. 82:184, 1907.

According to Moynihan and others, paraduodenal hernia is believed to be due to the intrusion of a loop of small intestine into one of the nine peritoneal fossae which occur near the duodenojejunal flexure or in relation to the mesenteries.<sup>30</sup> Andrews<sup>31</sup> disagreed most emphatically with this conception, however, for the following reasons:

1. A differential pressure is utterly lacking; the pressure in the main cavity can never be higher than the pressure within the pouch. No vis a tergo to account for the formation or growth of such a hernia is present.

2. There are literally hundreds of similar folds and fossae in the peritoneum, many of which are larger, and they are practically never the sites of such hernias.

3. In all but a small number of the cases reported the degree of herniation has been total or subtotal. How can one conceive of a force which would, once begun, practically always continue to act until the intestine had been segregated into a sac, even when the rest of the abdomen was empty?

Andrews concluded that so-called paraduodenal hernia is a congenital anomaly due to the imprisonment of the small intestine beneath the mesentery of the developing colon. Papez did not give as his belief that even this is adequate to account for all the conditions usually seen. Papez, who based his deductions on a condition observed at autopsy (fig. 9), stated the opinion that what corresponds to paraduodenal hernia is due to an exocelom which, with its intestinal contents, is drawn en masse into the general abdominal cavity by adhesions at the abdominal orifice of the exocelom to the duodenum (fig. 1, 20; the entire small intestine from the duodenum on is normally found in the exocelom together with part of the large intestine). The exocelom then persists within the abdominal cavity. With the increase in size of the intestine the exocelom increases proportionally. In his case the linea alba was normal and the umbilicus was closed, so apparently only the peritoneal lining of the exocelom with the intestinal inclusion was pulled into the abdomen. The reason the cecum was not in the sac, Papez stated, was that the adhesions involved only the duodenum and its mesentery. He gave as his opinion that the position of this exocelom with its intestinal inclusion depends on the time at which the adhesions between the duodenum and the orifice of the sac developed. If adhesions formed before the rotation of the ascending colon to the right and thus pre-

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30. Moynihan, B. G. A.: *On Retro-Peritoneal Hernia (Being the Arris and Gale Lectures on the Anatomy and Surgery of the Peritoneal Fossae)*, ed. 2, New York, William Wood & Company, 1906.

31. Andrews, E.: *Surg., Gynec. & Obst.* 37:740, 1923.

vented it, the sac would of necessity come down on the right of the ascending colon and be suspended from the duodenum (figs. 9 and 10). If the adhesions did not form until after the rotation of the ascending colon, the sac would come down to the left of the ascending colon (fig. 11). These conditions he said correspond to so-called right and left paraduodenal hernias or retroperitoneal hernias. In 139 cases of paraduodenal hernia, 34 hernias were on the right and 105 on the left.<sup>32</sup>

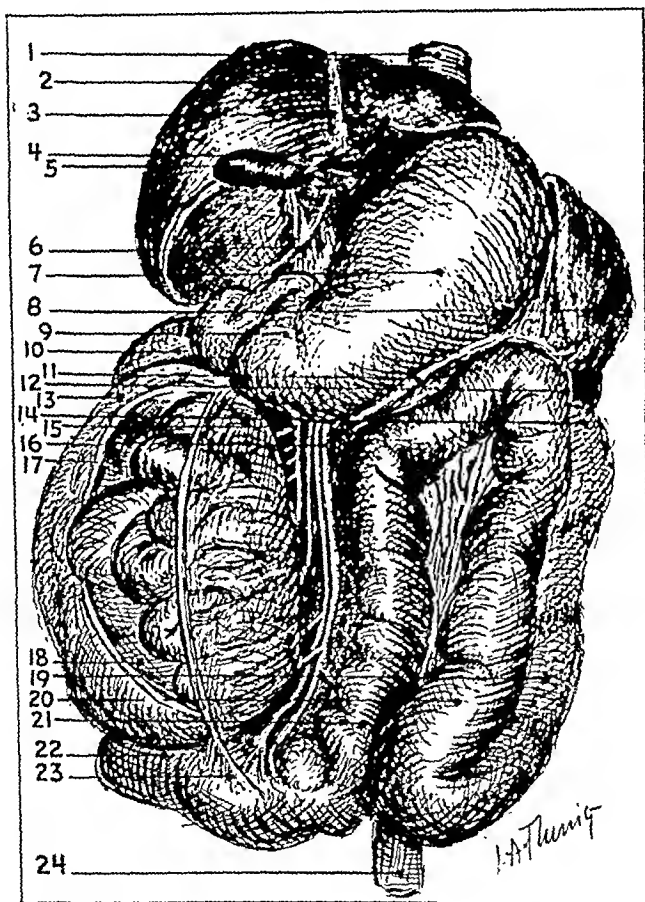


Fig. 9.—Copy of a drawing from actual case described by Papez<sup>14</sup> as an instance of a "rare intestinal anomaly of embryonic origin." By inference from the text there was a so-called right paraduodenal hernia or retroperitoneal hernia. I take the liberty of calling it a persistent intra-abdominal exocoelom with intestinal inclusion. 1 indicates the esophagus; 2, liver; 3, falciform ligament; 4, round ligament; 5, gallbladder; 6, hepatoduodenal ligament; 7, stomach; 8, spleen; 9, pylorus; 10, duodenum; 11, cut edge of the omentum; 12, kidney; 13, sac (peritoneal lining of exocoelom); 14, splenic flexure; 15, mesenteric vessels; 16, ileocolic vessels; 17, jejunum; 18, ileum; 19, transverse colon; 20, transverse colon; 21, ascending colon; 22, cecum; 23, adhesions; 24, pelvic colon.

The argument put forth by Andrews<sup>31</sup> as to the improbability of the old conception of paraduodenal hernia is so strong and the actual anatomic findings and the deductions made therefrom by Papez are so convincing that to me the later conception seems more plausible, and I have accordingly included it under the same heading as hernia into the umbilical cord. If Papez was correct, it is evident that in reality paraduodenal hernia is not a hernia. Furthermore, it brings so-called paraduodenal hernia and so-called hernia into the umbilical cord into close relationship. In one instance, there is a persistent exocelom with intestinal inclusion outside the abdomen; in the other, it is within the abdo-

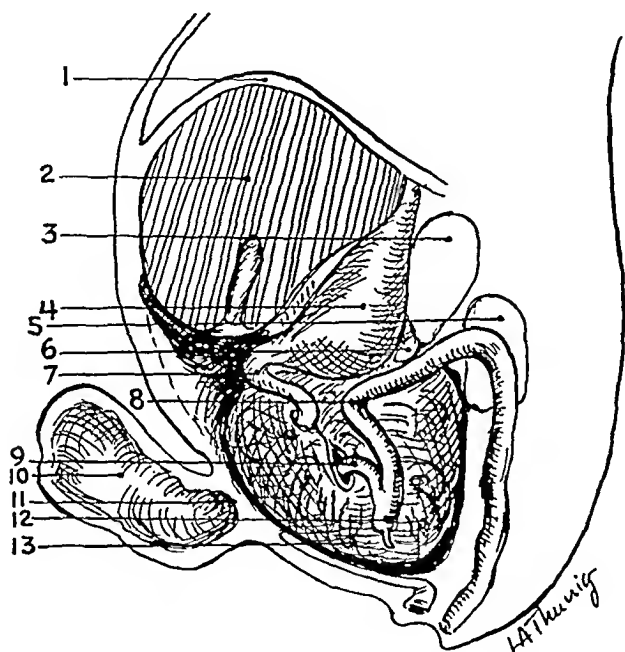


Fig. 10.—A copy of a diagrammatic sketch from the article by Papez<sup>14</sup> representing the formation of so-called right paraduodenal hernia. The ascending colon has not rotated to the right. 1 indicates the diaphragm; 2, liver; 3, adrenal glands; 4, stomach; 5, kidney; 6, spleen; 7, duodenum; 8, colon; 9, ileum; 10, exocelom minus a peritoneal lining; 11, umbilical opening; 12, cecum; 13, sac. The peritoneal lining of the exocelom with the intestinal inclusion has been reduced *en masse* from the umbilical cord, resulting in a persistent intra-abdominal exocelom with an intestinal inclusion. The colon is unrotated. (The position of the transverse and descending colon would probably differ from this sketch and be as shown in figure 9.)

men. If the foregoing statement is correct, the two conditions just cited are the two extremes of this particular type of anomaly; and if that is so, it is only a fair assumption that there must be some cases in which the anomaly has been arrested at some stage between the two extremes. Possibly the future will demonstrate that fact. There must

also be variations, depending on whether the exocoelom is empty or full, whether the umbilical ring is open or closed and whether or not the intestine is rotated. These are purely theoretical assumptions at present.

It was by the merest chance that I stumbled on the illuminating paper by Papez, for its title would not ordinarily include it in the list of references to be consulted concerning hernia into the umbilical cord. Furthermore, it appeared in a strictly scientific journal which would be less likely to be consulted than a clinical journal. It is for this reason that I have taken the liberty of quoting freely from the article and have

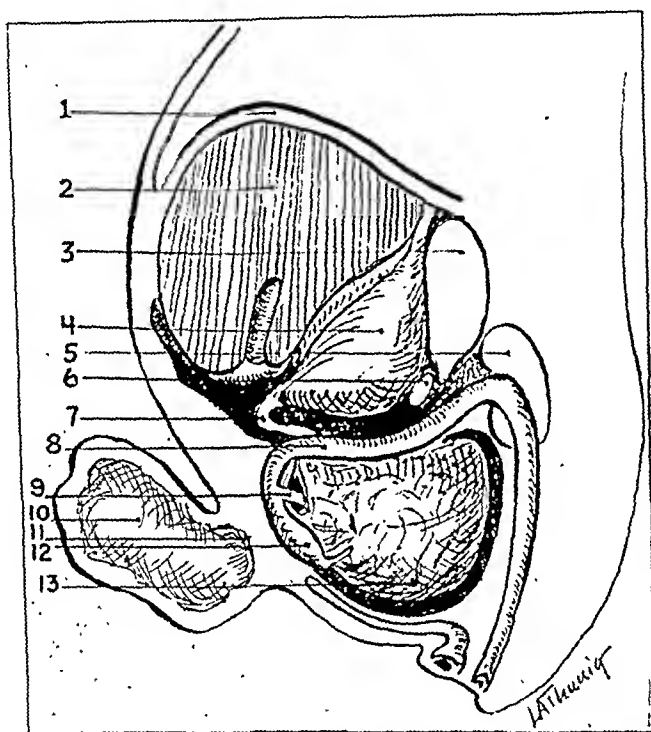


Fig. 11.—A diagrammatic drawing from the article by Papez<sup>14</sup> representing the formation of a so-called left paraduodenal hernia. The colon has rotated to the right. 1 indicates the diaphragm; 2, liver; 3, adrenal gland; 4, stomach; 5, kidney; 6, spleen; 7, duodenum; 8, colon; 9, ileum; 10, exocoelom wall minus its peritoneal lining; 11, umbilical opening; 12, cecum; 13, sac. The lining of the exocoelom with the intestinal inclusion has been reduced *en masse* from the umbilical cord, forming a persistent intra-abdominal exocoelom with an intestinal inclusion.

attempted to copy his drawings, so that so-called paraduodenal hernia may be linked up with other anomalies of the exocoelom, which I believe was the intention of Papez, even though he did not comment specifically on that point.

*Amniotic Umbilicus.*—In this condition there is a closing defect of the umbilical ring, and the deficiency is closed in with amnion reflected

from the cord. In at least one case there was a well defined ring at the umbilical site covered by a thin disk of fused amnion and peritoneum. The ring and disk became converted into scar tissue, and the umbilicus healed without difficulty.<sup>33</sup>

*Amniotic Linea Alba.*—This condition has heretofore not been given any specific name but has been described as a type of amniotic hernia, although it may exist without actual hernia. As the name implies, there is a deficiency of the linea alba with amniotic replacement, which may vary from a small area to practically the entire anterior abdominal wall. That it may exist without protrusion of the viscera has been shown by one case, Carrington Williams',<sup>11</sup> in which there existed in a 2 day old Negro child a congenital deficiency about the umbilicus about 3 inches

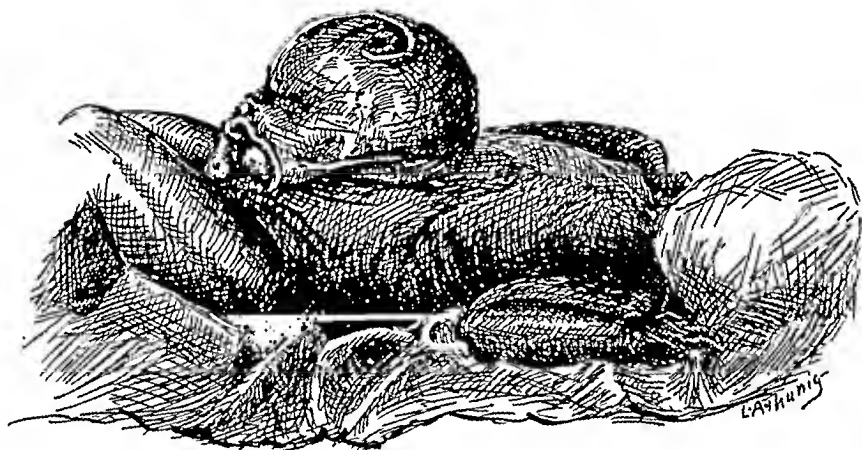


Fig. 12.—A sketch (with artist's liberties) of the photograph of an infant with an amniotic hernia (the case reported on by Dr. H. Wellington Yates), as shown in Cullen's<sup>34</sup> textbook entitled "Diseases of the Umbilicus."

(7.5 cm.) in diameter. This was covered by a transparent membrane, through which the intestine could be seen; but there was no protrusion.

*Amniotic Hernia.*—In this condition there is a primary amniotic linea alba with secondary actual herniation. Not only intestine but parts of or entire organs which normally develop within the true abdominal cavity have been found in these hernias. These are true hernias and may progress after birth.<sup>34</sup> Several references covering cases of amniotic hernia have already been cited.

33. Nicaise, E., in Dictionnaire encyclopédique des sciences médicales, Paris, V. Masson & fils, 1881, vol. 15, p. 140. Tordens: Clinique, Bruxelles 111:353. 1889.

34. Cullen,<sup>7</sup> p. 462.

## SUMMARY

*Case Report.*—It is shown that even a premature infant, weighing 3 pounds and 2 ounces (1,364 Gm.), forty minutes after birth may stand a major surgical procedure well, and with a condition such as was present immediate operation offers the best chance for recovery.

In this case certain conditions, not definitely determined, prevented reduction of the intestine into the abdomen even when no restricting ring of any kind was present.

The choice of overcoming this failure at reduction lay between removing the cause, with consequent handling of the intestine, or reducing the intestine in the sac. The latter method was chosen, and the postoperative course was smooth, with no gastro-intestinal disturbance immediately or during the following three years. A roentgenogram made when the child was 3 years old showed that the cecum was in the normal position.

The roentgenogram showed also an incomplete rotation of the transverse colon and upper end of the descending colon. This brings up the important question of the relationship of the normal or abnormal behavior of the exocolon and its contents and the process of intestinal rotation; also the determination of whether the abnormal behavior of the exocolon and its contents is the primary factor in the abnormal rotation, or at least some phases of it, or vice versa. To the best of my knowledge a roentgenogram has never been made in connection with such a case.

*Nomenclature and Classification.*—The present nomenclature is inaccurate. It does not give an insight into the actual anatomic or embryologic etiology of the conditions.

The nomenclature which is suggested, though rather wordy, does apply to the conditions named on an anatomic basis.

The classification, though possibly incomplete, covers the six conditions named and groups them in a systematic and anatomically orderly fashion.

The classification, irrespective of its merits or demerits, cannot be other than helpful to those seeking information in the literature on the six conditions included, which are shown to be closely related anomalies.



# QUANTITATIVE STUDIES ON CONGENITAL CLEFTS OF THE LIP

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AND

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MINNEAPOLIS

Previous studies<sup>1</sup> indicate that cleft palate consists not of an underdevelopment of tissue but of an abnormal displacement of the fully developed parts of the palate. It was also demonstrated that there is no tendency for the deformity to increase after birth. Measurements of the faces of children with clefts of the lip were so taken as to indicate the position of various parts of the nose in regard to the tragus of the ear and the position of the margins of the clefts in regard to the tragus. An analysis of these measurements is here reported.

This investigation was made to determine how much displacement of tissues had occurred in these children and also to find if such displacement is modified with age on account of unequal growth or continued unopposed muscle pull.

The measurements were made on the same children whose palates were previously measured,<sup>1</sup> i. e., ninety-one normal children and fifty-seven children with congenital clefts of the lip and palate. The cleft was bilateral in fourteen and on the left side in twenty-six and on the right side in seventeen.

The measurements analyzed in this paper are indicated in the accompanying illustration. They were taken from the tragus of the ear to the midline of the upper lip in the normal child and to the edge of the cleft in the maldeveloped child; in both the normal and the maldeveloped child the measurements were made from the tragus of the ear to the side of the nose, from the tragus of the ear to the midline or tip of the nose and from the tragus of the ear to the nasion, respectively.

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From the Department of Surgery of the University of Minnesota.

Aided by a grant from the Graduate School Fund for Medical Research, University of Minnesota.

1. Peyton, William T.: Dimensions and Growth of the Palate in the Normal Infant and in the Infant with Gross Maldevelopment of the Upper Lip and Palate, *Arch. Surg.* 22:704-737 (May) 1931; Dimensions and Growth of the Palate in Infants with Maldevelopment of the Upper Lip and Palate, *Am. J. Dis. Child.* 47:1265-1268 (June) 1934.

Regressive lines,  $y = a - bx$ , have been fitted by the pearsonian correlation technic to the data for each dimension and the crown-heel length,<sup>2</sup> the material being divided into the following categories:

1. Bilateral cleft lip and palate
  - (a) Data for left side
  - (b) Data for right side
2. Cleft of lip and palate on left side
  - (a) Data for left side
  - (b) Data for right side
3. Cleft of lip and palate on right side
  - (a) Data for left side
  - (b) Data for right side
4. Normal lip and palate

An average of the measurements of the left and right sides was used

5. All unilateral clefts of the lip and palate
  - (a) Measurements on the cleft side
  - (b) Measurements on the noncleft side

The results of comparison of the means and the coefficients of regression ( $b^3$ ) are given in table 2. The regression coefficient ( $b$ ) is the slope of the line, and therefore it measures the rate of increase with an increase in the crown-heel length. A significant difference in the coefficients of regression would indicate that the rate of growth is not the same. However, in none of these comparisons of the regression coefficients is  $P$  less than 0.16, which means that there are in no two groups compared more than sixteen chances in a hundred that a true difference in rate of growth occurs.

Since the rates of growth are the same, the midpoint of the regression lines or the means for the various groups may be used to compare the actual size of each dimension. Such a comparison demonstrates that all the measurements taken are shorter in the child with a cleft of the lip and palate. That there is not a significant difference in the size of the head in relation to the length of the body between the normal child and the child with a cleft has been previously demonstrated.

Although there is no significant difference in the measurements for the right and the left side of the normal child or of the child with bilateral cleft of the lip, still the averages for the left side are smaller in every case except one, the average for the left auriculolabial measurement in the normal child being slightly longer. This might be due to some constant error in the technic of taking these measurements. The number of measurements is too small to be conclusive, but it is sug-

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2. The statistical analysis was done under the direction of Dr. Edith Boyd, of the Department of Anatomy.

3.  $b = r_{xy} \frac{\sigma_y}{\sigma_x}$   $a = y + \sigma_x$

TABLE 1.—Results of Measurements on One Hundred and Forty-Eight Children

Crown- Heel Length, Cm.	Age, Days	Auriculo-Alveolar Measurement, Cm.		Auriculonasal (Side) Measurement, Cm.		Auriculonasal (Midline) Measurement, Cm.		Auriculonasal Measurement, Cm.	
		Left	Right	Left	Right	Left	Right	Left	Right
A. Normal Children									
45.7	10	7.7	7.3	6.7	6.8	8.0	8.1	7.8	8.2
48.8	12	8.0	7.5	7.2	6.9	8.7	8.1	8.1	8.3
49.0	2	...	...	7.1	7.4	8.5	8.4	8.0	8.2
49.2	1	9.0	9.1	7.7	7.3	9.1	9.0	8.9	8.5
49.3	16	8.5	8.4	7.3	7.3	8.5	8.5	8.3	8.3
49.3	10	8.6	8.9	7.8	7.8	8.9	9.2	8.7	8.3
50.0	29	8.0	8.0	6.7	6.6	7.8	7.9	8.3	8.1
50.2	3	...	...	7.1	7.1	8.5	8.3	8.5	8.4
50.4	10	8.1	8.9	6.9	7.6	8.1	8.8	8.1	8.2
51.5	4	8.5	8.5	7.3	7.6	8.6	9.0	8.6	8.9
51.7	16	8.4	9.0	7.5	7.5	9.0	9.2	8.4	8.9
51.8	10	8.5	8.3	7.4	7.4	8.8	8.7	8.5	8.5
52.1	14	9.0	8.9	7.5	7.7	9.2	9.0	8.8	8.8
52.5	40	8.5	9.0	7.5	7.8	9.0	9.0	9.0	9.0
52.6	53	8.0	8.2	7.4	7.2	8.6	8.8	8.5	8.4
52.7	0	8.8	8.9	7.6	7.4	9.3	9.3	8.8	8.7
52.7	66	8.6	8.3	7.3	7.3	9.0	9.0	...	...
52.9	6	8.2	8.4	7.0	7.2	8.6	8.7	8.3	8.3
53.1	35	9.3	9.1	7.8	7.8	9.3	9.1	9.7	9.1
53.1	32	8.7	8.9	7.6	7.7	8.9	9.0	9.0	9.0
53.4	5	9.0	9.5	8.3	8.2	9.4	9.8	9.2	9.2
53.7	66	8.6	9.1	7.6	7.6	9.2	9.3	8.9	9.6
54.2	20	8.5	8.8	7.4	8.0	8.8	9.3	8.5	9.2
54.3	36	9.5	9.2	8.2	8.0	10.1	9.4	10.6	9.3
54.6	37	9.7	9.5	8.5	8.5	9.8	10.0	9.5	10.1
55.2	36	9.0	8.6	8.5	7.6	9.5	8.7	9.0	8.5
55.4	47	8.2	8.1	7.5	7.9	9.2	8.7	9.5	9.5
55.6	60	9.6	9.1	8.5	8.5	9.1	9.5	9.7	9.5
56.1	63	9.5	9.6	8.5	8.5	9.5	9.2	9.1	9.0
56.3	158	9.2	9.0	8.5	8.4	9.5	9.6	9.2	9.3
56.3	68	9.5	9.5	8.3	8.4	9.8	10.0	9.8	9.8
56.6	48	8.8	9.0	7.7	7.8	9.5	9.2	9.3	9.3
56.8	86	9.5	9.7	8.5	8.5	10.0	10.5	9.4	9.9
57.3	51	9.9	9.9	8.4	8.5	10.2	10.0	9.1	9.4
57.5	91	10.2	9.7	8.0	8.5	10.0	9.8	9.6	9.8
57.9	83	10.1	9.9	8.8	8.7	10.0	10.1	9.7	9.6
57.9	87	9.0	9.3	7.8	8.2	9.4	9.6	9.7	9.2
58.2	82	10.0	10.0	8.8	9.4	10.3	10.2	10.3	10.5
58.5	85	9.5	10.0	8.9	8.9	9.6	10.2	10.0	10.0
58.7	83	9.7	9.2	8.9	8.5	9.6	9.8	10.0	10.0
58.9	124	10.3	9.7	8.9	8.2	10.5	10.2	10.0	10.0
59.0	119	9.7	9.5	8.6	8.2	10.1	9.6	9.1	9.5
59.0	136	9.0	9.2	7.9	8.0	9.0	9.1	9.4	9.3
59.0	75	9.0	9.0	8.1	8.0	10.0	9.8	9.6	10.0
59.3	45	9.9	9.9	8.8	8.7	10.0	10.2	9.9	10.0
59.5	143	9.8	9.8	8.9	8.5	10.5	10.0	10.3	9.8
59.9	105	10.3	10.2	8.8	8.8	10.6	10.6	10.8	11.0
60.1	113	9.1	9.0	8.4	8.0	10.0	9.6	10.0	9.4
60.3	99	8.6	9.4	8.3	8.4	9.6	9.5	9.3	9.6
60.4	101	10.0	10.2	8.6	8.8	9.5	10.1	9.5	9.5
60.5	93	9.6	9.4	8.3	8.2	10.0	10.0	10.2	10.2
60.5	79	9.8	9.6	8.6	8.4	9.8	9.8	...	...
60.8	106	9.8	9.5	8.9	8.4	9.9	9.5	9.3	9.4
61.0	152	10.2	10.5	9.0	9.2	10.5	10.7	10.1	10.3
61.1	90	9.6	9.7	8.2	8.4	9.8	10.1	9.3	9.2
61.7	134	9.0	9.2	8.5	8.5	9.5	9.5	9.0	9.6
61.7	140	10.0	10.0	7.0	8.0	10.0	10.5	...	...
61.8	162	9.8	9.9	8.4	8.8	9.4	9.8	9.3	9.9
61.9	109	9.9	9.8	8.4	9.0	10.0	10.5	10.1	10.0
62.0	68	9.5	9.3	8.2	8.4	9.8	9.9	9.5	9.6
62.7	115	9.5	9.5	8.4	8.4	10.0	10.1	10.0	9.8
62.9	141	9.8	10.0	9.3	9.5	10.5	10.2	10.5	10.2
63.6	193	10.3	9.6	8.8	8.2	10.2	9.8	9.5	9.4
63.7	176	10.9	10.6	8.8	9.5	10.3	10.5	10.0	10.0
64.1	135	9.6	9.8	8.5	8.5	10.6	10.1	10.3	10.5
64.4	259	11.0	11.0	9.0	9.4	10.6	10.9	11.2	11.2
64.5	100	9.9	10.0	8.9	8.9	10.0	10.2	10.5	10.5
64.8	203	11.0	10.5	9.8	9.7	10.8	11.1	11.0	11.3
65.1	219	10.3	10.7	9.2	9.4	10.6	10.8	11.0	11.0
65.7	198	10.2	10.0	9.0	9.0	10.4	10.0	9.9	10.1
65.7	141	10.5	9.8	9.4	8.5	11.0	10.2	11.0	11.3
65.7	213	9.5	9.5	8.1	8.4	9.7	10.5	10.0	10.1
66.6	168	10.2	10.5	8.9	9.3	10.1	10.8	10.5	11.0
66.8	295	10.6	11.1	9.2	9.3	10.6	11.3	10.5	11.0
66.9	241	10.1	10.1	9.0	8.8	10.2	10.0	10.2	10.5
67.0	179	10.0	10.0	9.3	9.1	10.2	10.5	10.0	10.0
68.0	286	10.5	10.1	9.0	9.2	10.2	10.6	10.5	10.2
68.0	375	10.5	10.2	8.8	9.1	10.3	10.4	10.3	10.3
68.2	188	9.3	10.4	8.4	9.0	10.0	10.6	9.2	10.2
68.5	278	10.2	10.0	9.0	9.0	10.4	10.0	10.0	10.2

TABLE 1.—Results of Measurements on One Hundred and Forty-Eight Children—  
Continued

Crown- Heel Length, Cm.	Age, Days	Auriculo-Alveolar Measurement, Cm.		Auricleonasal (Side) Measurement, Cm.		Auricleonasal (Midline) Measurement, Cm.		Auricleonasal Measurement, Cm.	
		Left	Right	Left	Right	Left	Right	Left	Right
69.0	313	10.5	10.5	9.2	9.0	11.0	11.0	11.1	11.2
69.1	283	9.6	9.5	9.2	9.0	10.0	10.5	10.5	10.5
69.3	238	10.5	10.0	9.0	9.0	10.8	10.3	11.5	10.0
70.0	272	10.0	10.0	9.0	8.4	10.4	10.2	10.4	10.5
70.2	238	9.9	9.8	7.8	8.2	10.2	10.0	10.5	10.2
70.7	282	10.4	10.4	9.0	8.9	10.5	10.4	10.4	10.0
71.5	344	10.3	10.5	9.5	9.0	10.5	10.2	10.3	10.7
72.5	330	10.6	10.5	9.7	9.3	11.0	11.2	10.6	10.5
73.8	315	10.6	10.8	9.5	9.3	10.5	11.0	10.5	11.1
75.4	259	11.2	11.2	9.5	9.5	11.2	11.5	11.2	11.3
75.5	362	11.0	11.0	9.8	10.0	11.5	11.1	11.1	11.2
B. Maldeveloped Children									
1. Bilateral Clefts									
47.5	11	7.2	7.2	7.1	6.7	8.8	8.8	8.2	8.5
50.3	3	7.2	7.1	6.8	6.7	8.6	8.5	8.5	8.5
52.1	28	7.4	7.4	7.1	7.0	8.9	8.9	8.7	8.7
52.3	25	7.1	7.1	7.0	6.9	8.7	9.0	8.0	8.8
52.7	46	7.6	8.1	7.3	7.6	8.7	9.5	8.6	9.3
52.8	72	7.4	7.4	7.0	7.2	8.7	9.1	8.8	9.1
53.0	52	7.9	7.5	7.1	7.3	9.0	8.5	8.7	8.5
53.7	43	7.3	8.0	7.0	7.2	9.1	9.0	8.8	9.1
54.0	30	8.0	7.5	7.5	7.2	9.6	9.6	9.5	9.5
55.0	18	8.0	7.5	7.5	7.2	9.6	8.6	9.0	8.8
56.6	52	7.5	8.2	7.1	7.5	9.1	9.2	9.2	9.5
57.5	95	7.6	8.2	9.1	7.5	9.0	9.5	9.5	9.5
58.5	67	9.0	8.8	8.0	8.3	10.2	11.0	9.8	10.3
59.0	76	7.6	8.3	7.1	7.7	8.6	10.0	9.2	10.0
2. Clefts of Left Side									
46.0	8	5.4	6.2	5.5	5.4	7.5	6.5	7.4	7.0
48.0	11	7.9	8.0	7.2	7.3	9.4	9.0	9.2	9.0
50.9	59	7.4	8.3	7.1	6.8	9.1	8.4	8.9	8.6
51.2	34	7.5	8.1	7.0	7.3	9.1	8.5	8.3	9.3
51.4	42	7.5	8.8	7.0	6.8	9.3	8.2	9.0	8.5
53.6	71	8.0	8.6	7.2	7.5	9.4	8.8	8.8	8.9
54.0	20	7.6	8.0	7.4	6.8	9.6	8.2	9.2	8.6
55.3	63	8.3	7.8	7.1	7.3	8.5	9.7	9.0	9.6
56.5	49	8.0	9.2	7.8	7.6	9.5	9.3	9.6	9.8
56.7	47	8.3	8.5	7.4	8.0	9.0	10.2	9.3	9.5
56.8	56	7.9	8.0	7.5	7.7	9.3	9.2	9.2	8.6
56.9	21	8.3	9.1	8.2	7.8	10.1	9.4	9.8	9.7
57.8	89	7.8	8.4	7.2	7.2	9.4	8.6	8.8	9.2
57.8	78	7.9	8.0	7.2	7.2	9.5	8.5	9.0	9.2
58.7	64	8.5	9.0	7.5	7.5	9.6	8.8	9.0	9.0
58.9	81	7.6	8.2	7.1	7.0	9.2	8.5	9.0	8.5
59.7	95	8.5	9.1	8.4	7.9	10.1	9.2	9.5	9.5
60.1	74	9.0	9.9	8.2	8.0	10.1	9.9	9.6	9.6
61.7	240	8.8	9.6	8.3	8.4	....	....	9.5	10.2
63.4	190	8.5	9.2	8.0	7.5	10.3	9.0	10.0	9.3
66.1	183	8.6	9.5	8.4	7.8	10.3	9.5	9.5	9.5
66.4	278	9.5	9.1	8.3	8.6	10.0	10.1	10.0	9.8
67.2	225	8.6	9.0	8.4	8.2	10.0	10.0	10.0	9.8
67.6	218	10.0	10.3	9.5	9.0	11.2	10.4	10.6	10.7
70.5	380	9.5	10.0	9.0	8.7	11.0	10.5	10.5	10.0
75.1	391	10.0	10.9	9.4	9.3	11.4	11.0	10.7	11.0
3. Clefts of Right Side									
50.0	10	8.4	7.8	6.9	7.4	8.7	9.6	8.1	9.1
50.9	13	7.1	7.2	6.3	6.6	8.3	8.7	8.4	8.6
51.6	16	8.4	8.0	7.3	7.6	9.0	9.5	8.5	9.2
51.7	77	8.8	8.5	7.5	8.1	9.0	9.5	8.9	9.6
52.0	48	8.5	7.0	7.0	6.8	8.5	10.2	9.0	9.3
52.2	41	9.3	8.5	7.5	8.0	9.5	10.0	9.5	9.3
53.6	40	8.8	8.1	7.5	8.3	9.0	9.6	9.2	9.7
56.2	50	9.7	8.7	8.1	8.3	9.6	10.2	10.1	9.8
56.9	121	9.1	7.7	7.5	7.4	9.1	9.0	8.9	9.2
57.0	71	9.4	8.9	8.1	8.1	9.7	10.4	9.6	9.7
57.2	97	8.7	8.4	7.3	8.0	9.4	10.0	9.0	9.7
57.6	76	9.4	8.6	8.5	8.6	10.0	10.5	10.3	10.0
58.5	48	10.0	9.0	8.2	8.5	10.5	11.0	10.0	10.4
59.2	101	8.9	8.0	7.4	8.0	9.1	9.9	9.1	9.8
59.5	111	7.9	8.4	8.0	7.8	9.8	9.9	9.7	9.8
60.5	143	9.0	8.2	9.0	8.2	9.2	10.6	9.4	9.8
63.7	232	8.8	8.8	7.2	8.0	8.9	10.0	9.2	10.0

TABLE 2.—*Comparison of Means and Coefficients of Regression*

Measurements	n	$y \pm \sigma_y$	Diff. $\pm$ P.E.	R.	P.	$b \pm \sigma_b$	Diff. $\pm$ P.E.	R.	P.
<b>A. Normal Child</b>									
Auriculoalabial (midline), 89 cases	R L 3,8578 3,2944	9,5584 $\pm$ 0.0828 9,5607 $\pm$ 0.0860	-0.0023 $\pm$ 0.1194	0.0193	0.98	0.0948 $\pm$ 0.0070 0.1042 $\pm$ 0.0063	-0.0094 $\pm$ 0.0095	0.9916	0.32
Auriculonasal (side), 91 cases	R L 3,1869 2,9579	8,3813 $\pm$ 0.0737 8,3626 $\pm$ 0.0796	0.0187 $\pm$ 0.1099	0.1702	0.87	0.0867 $\pm$ 0.0063 0.0897 $\pm$ 0.0063	-0.0030 $\pm$ 0.0093	0.3246	0.75
Auriculonasal (midline), 91 cases	R L 4,0433 4,1503	9,8132 $\pm$ 0.0820 9,7769 $\pm$ 0.0792	0.0363 $\pm$ 0.1141	0.3183	0.75	0.0963 $\pm$ 0.0064 0.0934 $\pm$ 0.0061	0.0029 $\pm$ 0.0089	0.3255	0.75
Auriculonasal, 88 cases	R L 3,4479 3,6056	9,7170 $\pm$ 0.0912 9,6739 $\pm$ 0.0910	0.0431 $\pm$ 0.1283	0.3346	0.74	0.1046 $\pm$ 0.0070 0.1012 $\pm$ 0.0075	0.0033 $\pm$ 0.0102	0.3267	0.74
<b>B. Maldeveloped Child</b>									
<b>1. Bilateral Clefts</b>									
Auriculoalabial, 14 cases	R L 0,4309 2,9009	7,7357 $\pm$ 0.1350 7,6286 $\pm$ 0.1253	0.1071 $\pm$ 0.1846	0.5902	0.56	0.1355 $\pm$ 0.0270 0.0866 $\pm$ 0.0366	0.0489 $\pm$ 0.0460	1.0752	0.29
Auriculonasal (side)	R L 1,2532 3,1719	7,2957 $\pm$ 0.1093 7,2500 $\pm$ 0.0908	0.0357 $\pm$ 0.1442	0.2476	0.81	0.1119 $\pm$ 0.0209 0.0756 $\pm$ 0.0233	0.0362 $\pm$ 0.0313	1.1564	0.25
Auriculonasal (midline)	R L 1,2956 5,5786	9,2286 $\pm$ 0.1732 9,0429 $\pm$ 0.1192	0.1857 $\pm$ 0.2102	0.8834	0.38	0.1452 $\pm$ 0.0442 0.0642 $\pm$ 0.0376	0.0810 $\pm$ 0.0581	1.3043	0.16
Auriculonasal	R L 1,0421 2,5063	9,1500 $\pm$ 0.1456 8,9571 $\pm$ 0.1135	0.1929 $\pm$ 0.1846	1.0450	0.30	0.1503 $\pm$ 0.0272 0.1196 $\pm$ 0.0201	0.0307 $\pm$ 0.0339	0.9070	0.37
<b>2. Clefts of Left Side</b>									
Auriculoalabial, 26 cases	R L 2,2171 1,4962	8,8000 $\pm$ 0.1837 8,2654 $\pm$ 0.1806	0.5346 $\pm$ 0.2577	2.0745	0.04	0.1120 $\pm$ 0.0153 0.1152 $\pm$ 0.0139	-0.0032 $\pm$ 0.0211	0.1504	0.89
Auriculonasal (side), 26 cases	R L 1,3357 2,9241	7,6385 $\pm$ 0.1550 7,7423 $\pm$ 0.1664	-0.1038 $\pm$ 0.2274	0.4565	0.65	0.0977 $\pm$ 0.0123 0.1093 $\pm$ 0.0117	-0.0116 $\pm$ 0.0170	-0.6810	0.50
Auriculonasal (midline), 26 cases	R L 3,8576 4,1375	9,1760 $\pm$ 0.1870 9,6760 $\pm$ 0.1691	-0.5000 $\pm$ 0.2481	2.0153	0.05	0.1066 $\pm$ 0.0163 0.0992 $\pm$ 0.0128	0.0074 $\pm$ 0.0211	0.3495	0.73
Auriculonasal, 26 cases	R L 4,2373	9,3231 $\pm$ 0.1526 9,3615 $\pm$ 0.1375	-0.0384 $\pm$ 0.2054	0.1870	0.83	0.0852 $\pm$ 0.0144 0.0872 $\pm$ 0.0108	0.0010 $\pm$ 0.0180	0.0580	0.95
<b>3. Clefts of Right Side</b>									
Auriculoalabial, 17 cases	R L 3,9703 5,4324	8,2235 $\pm$ 0.1323 8,8333 $\pm$ 0.1606	-0.6118 $\pm$ 0.2084	2.9360	....	0.0762 $\pm$ 0.0312 0.0610 $\pm$ 0.0418	0.0152 $\pm$ 0.0522	0.2920	0.77

Auriculonasal (side), 17 cases	R	3.088	7.847 $\pm$ 0.1297	1.2914	0.19	0.070 $\pm$ 0.0311	-0.0200 $\pm$ 0.0171	0.1270	0.67
	L	2.6334	7.8039 $\pm$ 0.1358			0.0909 $\pm$ 0.0354			
	R	5.352	9.0176 $\pm$ 0.1352	3.5251	....	0.0728 $\pm$ 0.0325	0.0069 $\pm$ 0.0153	0.1713	0.88
	L	5.570	9.2329 $\pm$ 0.1312			0.0639 $\pm$ 0.0325			
Auriculonasion, 17 cases	R	5.173	9.5839 $\pm$ 0.1003	2.0653	0.04	0.0791 $\pm$ 0.0189	-0.0017 $\pm$ 0.0379	0.1270	0.90
	L	4.5342	9.2294 $\pm$ 0.1416			0.0312 $\pm$ 0.0323			
Normal Child with Pathologic Side of Maldeveloped									
Auriculolabial	N*	3.5800	9.5596 $\pm$ 0.0796		....	0.0901 $\pm$ 0.0017	-0.0037 $\pm$ 0.0136	0.2959	0.78
	P*	2.3114	8.2488 $\pm$ 0.1212	9.6940		0.1031 $\pm$ 0.0127			
	N	3.0912	8.3720 $\pm$ 0.0349	4.6163	....	0.0852 $\pm$ 0.0046	-0.0062 $\pm$ 0.0131	0.1726	0.61
	P	2.3565	7.7907 $\pm$ 0.1133			0.0916 $\pm$ 0.0123			
Auriculonasal (side)	N	4.1156	9.7951 $\pm$ 0.0370	0.1631	0.86	0.0918 $\pm$ 0.0044	0.0998 $\pm$ 0.0111	0.6505	0.19
	P	4.8840	9.7788 $\pm$ 0.1129			0.0570 $\pm$ 0.0131			
Auriculonasion	N	3.5305	9.0955 $\pm$ 0.0644	2.1521	0.03	0.1024 $\pm$ 0.0051	0.0296 $\pm$ 0.0116	2.2576	0.22
	P	5.0358	9.4512 $\pm$ 0.0935			0.0763 $\pm$ 0.0104			
Normal Child with Normal Side of Maldeveloped									
Auriculolabial	N	3.5800	9.5596 $\pm$ 0.0797	5.2823	....	0.0901 $\pm$ 0.0017	0.0029 $\pm$ 0.0162	0.1770	0.56
	P	3.2523	8.3140 $\pm$ 0.1279			0.0852 $\pm$ 0.0155			
Auriculonasal (side)	N	3.0912	8.3720 $\pm$ 0.0349	6.0032	....	0.0852 $\pm$ 0.0046	-0.0031 $\pm$ 0.0132	0.2579	0.79
	P	2.3526	7.6256 $\pm$ 0.1116			0.0916 $\pm$ 0.0123			
Auriculonasal (midline)	N	4.1156	9.7951 $\pm$ 0.0370	4.3239	....	0.0918 $\pm$ 0.0044	0.0010 $\pm$ 0.0151	0.1248	0.90
	P	3.5661	9.2071 $\pm$ 0.1235			0.0229 $\pm$ 0.0117			
Auriculonasion	N	3.5305	9.0955 $\pm$ 0.0644	3.2703	....	0.1023 $\pm$ 0.0051	0.0185 $\pm$ 0.0137	1.3465	0.18
	P	4.4297	9.2860 $\pm$ 0.1083			0.0813 $\pm$ 0.0125			
Pathologic with Normal Side of Maldeveloped									
Auriculolabial	P	2.3114	8.2488 $\pm$ 0.1213	3.2066	....	0.1031 $\pm$ 0.0127	0.0067 $\pm$ 0.0201	0.3920	0.74
	N	3.2325	8.3140 $\pm$ 0.1279			0.0909 $\pm$ 0.0155			
Auriculonasal (side)	P	2.3565	7.7907 $\pm$ 0.1133	1.0383	0.30	0.0911 $\pm$ 0.0123	0.0023 $\pm$ 0.0174	0.1608	0.87
	N	2.3526	7.6256 $\pm$ 0.1116			0.0216 $\pm$ 0.0123			
Auriculonasal (midline)	P	4.8840	9.7788 $\pm$ 0.1129	3.3569	....	0.0852 $\pm$ 0.0131	-0.0078 $\pm$ 0.0179	0.3939	0.69
	N	3.5661	9.2071 $\pm$ 0.1235			0.0929 $\pm$ 0.0117			
Auriculonasion	P	5.0358	9.4512 $\pm$ 0.0935	1.1551	0.21	0.0763 $\pm$ 0.0104	-0.0051 $\pm$ 0.0165	0.4592	0.62
	N	4.4297	9.2860 $\pm$ 0.1083			0.0813 $\pm$ 0.0125			

\*N indicates normal and P, pathologic.

gestive of an actual difference due to shorter measurements on the left side. It is interesting to speculate that there may be some relation between short measurements on the left side and the predominance of clefts on that side.

The auriculolabial measurement is significantly shorter on the cleft side. This is to be expected, since the cleft is not in the midline. The difference is approximately 0.5 cm.

The auriculonasal (side) measurement in cases of unilateral cleft was not demonstrated to be significantly shorter on either side, but the average in cases of cleft on the right or left side was shorter on the noncleft side.

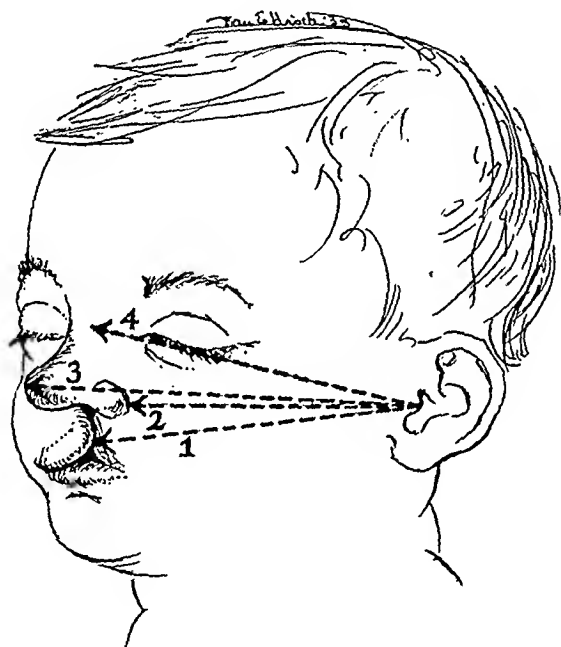


Diagram showing the measurements analyzed: 1, the auriculolabial measurement; 2, the auriculonasal (side) measurement; 3, the auriculonasal (midline) measurement, and 4, the auriculonasion measurement.

The auriculonasal (midline) measurement is significantly shorter on the noncleft side, demonstrating that the tip of the nose is shifted approximately 0.5 cm. toward the noncleft side.

The auriculonasion measurement in cases of unilateral cleft was not demonstrated to be significantly different, but in cases of cleft on the right or left side the average auriculonasion measurement was shorter on the noncleft side.

Considered as a whole, these findings suggest that the entire nose is slightly shifted to the noncleft side, the tip of the nose being shifted much more than any other part. Analysis of measurements for a larger

series of children would probably show significant differences in these dimensions where it is here indicated by the constant direction of differences.

#### COMMENT

The margin of error in the comparative measurements of the normal and cleft palate<sup>1</sup> must be negligible because the measurements were made on fixed tissues. The margin of error in the measurements of the face of the normal child and of the child with a cleft lip here presented are more variable because the measurements are made on movable tissues. Factors of muscle pull and personal interpretation enter more definitely into this study. The conclusions of the former study on the palate indicate that the tissues are all present but are out of contact. In this study there is in some instances a variance of from 2 to 4 mm. From a clinical standpoint of operative effort, measurement of from 2 to 4 mm., either in the deficiency of the tissue in the palate or in the width of a cleft, is a definite surgical problem. On the face, however, a difference of from 2 to 4 mm. between the normal and the abnormal face is of no moment, because of the movability of these tissues. The study of this material indicates that the deformity does not increase with growth. This is an important finding which must be checked, because if accepted or proved true it presents a proposition fundamental to surgical repair, viz., in a condition of apparent deficiency, the potentiality of future growth is inherent. Clinically, this proposition is widely supported, because, in the observation of a considerable number of cases in which repair of the deformities of the face has been neglected to later years, the tissues out of contact have grown with the body.

#### SUMMARY

The dimensions analyzed demonstrate no tendency for the deformity due to cleft of the lip to increase with growth, and rate of growth in the face of the child with cleft lip appears to be the same as that in the face of the normal child.

In the child with unilateral cleft of the lip the entire nose appears to be shifted toward the noncleft side, the tip of the nose being shifted approximately 0.5 cm., which is greater than the shift of any other part of the nose.



# UNUSUAL CARTILAGINOUS TUMOR FORMATION OF THE SKELETON.

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The purpose of this article is to report a few cases of cartilaginous tumor of the skeleton, which represent in part unusual forms of otherwise well known conditions (enchondroma, single osteochondroma and multiple cartilaginous exostoses) and in part an apparently rare form of a multiple intra-articular tumor formation which, to my knowledge, has not yet been described in the literature. The case which will be reported last is one of a true intra-articular osteochondroma, which developed in more than one joint on the basis of a peculiar hyperplastic change of joint cartilage and which had to be differentiated from similar formations as they develop typically in persons with hypertrophic arthritis and from other conditions usually considered as neoplastic changes of the joint capsule, such as chondromatosis of the joints.

As is so common in cases of cartilaginous tumor formation of the skeleton, besides the cartilaginous component a considerable amount of bony tissue was present. One is justified in speaking of the growth as a cartilaginous tumor, despite the fact that in some instances the bony component is prevalent, mainly because the cartilaginous portion represents the real active element in the tumor, the cellular proliferation of which results in the increase in size. The bony tissue replaces the cartilage; its significance is therefore merely secondary.

## REPORT OF CASES

### CASE 1.—*Enchondroma of the femur.*

A man aged 55 complained of pain in the region of the right hip. He had had periodic attacks of pain in the upper part of the right femur for the past eight years, which gradually became worse and interfered with his work as a farmer. The hip joint had never been stiff, and he had only a moderate limp for one year. There was no fever or loss of weight.

Physical examination revealed a smooth enlargement of the upper third of the right femur of hard bony consistency, which was moderately tender in a few places. The surrounding soft parts and the overlying skin were normal. There was no swelling of the inguinal lymph nodes. The motion in the hip joint was free in all directions, except for external rotation, which was slightly restricted. The Wassermann reaction was negative. Examination of the blood gave essentially normal results: red blood cells, 4,660,000; white blood cells, 9,700, and hemoglobin content, 90 per cent.

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A roentgenogram of the upper third of the right femur showed considerable enlargement, with very irregular bony structure. The old cortical bone had been entirely removed, and the expansion of the bone extended to the periosteal surface, where on the outer side a small prominence of irregular and porotic bony structure had formed. The inner architecture of the lesion was that of extremely coarse trabeculation and calcification with areas which were almost cystlike in appearance. There were some transverse zones of rarefaction running through the enlarged area, most likely representing incomplete fracture lines. The pathologic changes gradually extended upward and downward into normal bony tissue with



Fig. 1 (case 1).—Enchondroma of the femur in a man aged 55.

erosion of the cortical bone from within and considerable apposition of periosteal bone on the medial side of the cortical bone. The entire lesser trochanter had become invaded. There was no swelling of the soft tissue. Marked calcification of the wall of the femoral artery was present.

Two possibilities had to be considered on the basis of the roentgenographic and the clinical picture: The lesion could be either inflammatory or neoplastic. From the roentgenographic standpoint a chronic osteomyelitic lesion could produce such a picture, although the clinical history, with the absence of more acute symptoms and fever and the beginning of clinical manifestations rather late in life, spoke primarily against it. The roentgenogram, also, on more careful

examination, showed a few features which did not fit well into the common picture of osteomyelitis. The localization in the upper third of the femur would be an unusual site for pyogenic osteomyelitis. The amount of periosteal bone production was insignificant and did not correspond to the marked degree of bone destruction, if the latter were due to an inflammatory process. On this basis, a diagnosis of pyogenic osteomyelitis could be ruled out from a clinical and a roentgenographic standpoint.

There was nothing to suggest a specific inflammatory lesion, such as syphilitic osteomyelitis. The Wassermann reaction was negative, and a gummatous lesion would also have produced more periosteal reaction than was present in this case.

Among the neoplastic lesions, several had to be considered. The almost cystlike appearance of the lesion, with the blowing up and thinning out of the cortex, could suggest a benign giant cell tumor. Against it were the age of the patient (giant cell tumor usually occurs toward the end of the second or in the third decade of life) and the localization of the tumor (giant cell tumor is of epiphyseal origin and commonly situated in the lower end of the femur and not in the upper end). Still the possibility of an atypical giant cell tumor had to be kept in mind.

A diagnosis of osteogenic sarcoma could safely be ruled out because of the long duration of the lesion (at least eight years), although from the roentgenogram one could be reminded somewhat of the *forme géodique* of a central cystic diaphyseal sarcoma.

Along the same line, Ewing's tumor could be mentioned as a diaphyseal lesion, which in the chronic stage may resemble an inflammatory process, but there was no evidence clinically to substantiate such a diagnosis.

There remained one form of tumor which quite often is seated in the upper end of the diaphysis of the femur and which could explain the clinical as well as the roentgenographic picture. I mean the embryonal chondroma or enchondroma of the femur, which frequently is a silent tumor during the greater part of the patient's life, but at a later age it may show more marked proliferation of its cells and may even become a malignant chondroma. The irregular calcification, with areas which were almost cystlike in appearance, the erosion of the cortical bone from within and the relatively weak periosteal reaction were well compatible with the diagnosis of embryonal chondroma of the femur, with greater activity during the last eight years.

To arrive at a definite diagnosis, a biopsy was performed. The periosteum over the enlarged portion of the femur was smooth and thin. The cortical bone on the outside was thinned to about 1 mm., but it was in no place completely interrupted. The endosteal surface was eroded by a transparent gelatinous bluish white tissue, which was typical of embryonal chondroma or myxochondroma.

Histologically, the tumor tissue was characterized by starlike cells, with a loose, watery ground substance between the protoplasmic processes of the cells. The ground substance was slightly basophilic. In some areas the basophilia became more marked, and the cells assumed here more the spherical shape of cartilaginous cells. Owing to the interstitial growth of the tumor tissue with augmented intraosseous pressure, the bony tissue gradually disappeared as a result of osteoclastic resorption of bone. There was, however, everywhere a sharp borderline between the tumor and the bony tissue. The bone marrow formed a kind of fibrous capsule around the tumor tissue which imitated in many places a perichondrium. The configuration of the tumor toward the surrounding normal bone marrow was convex, corresponding to the pressure within the tumor tissue. The tumor became subdivided into many smaller lobules by stronger bony trabeculae. The convexity of the lobules was always turned toward the normal marrow spaces.

There was no infiltrative tumor growth, so that the haversian canals of the cortical bone were free from invasion by the tumor. Owing to continuous apposition of the periosteal bone, the cortical bone became gradually displaced toward the periphery, which, combined with the resorption of bone at the endosteal side, led, to the blowing up and thinning out of the cortical bone over the tumor. The roentgenographic diagnosis could thus be confirmed by biopsy.

In this case an enchondroma was being dealt with, which in many places still had the appearance of a myxoma, so that the classification as embryonal enchondroma seemed to be justified. There were no histologic signs of malignancy. The clinical history, with increasing pain and weakness of the leg, suggested, however, a more rapid growth within the last few years, so that the possibility of at least a mild local malignant growth had to be considered. Roentgen therapy was instituted. During two years' observation and frequent roentgenographic control examinations, no increase in the size of the lesion could be noted; it even seemed that there was a greater tendency to calcification. A long leg brace could gradually be discarded.

CASE 2.—*Osteochondroma ossis calcis.*  
A woman aged 45 first noticed a growth on her left heel eighteen years before the present examination. It started gradually and then became larger; the skin over it hardened, but never broke down. The patient was operated on eight times, the first time about fourteen years before and the last time about three years before the present examination. The tumor had recurred since and was growing slowly all the time. Recently it had extended to the outside of the foot.

On physical examination the skin over the left heel was found scarred in many places and firmly adherent to the underlying structures. There was an irregular knobby growth on the os calcis, especially on its inferior and posterior aspects, apparently also involving the cuboid bone and the base of the fifth metatarsal bone. The tumor was firm and solidly attached to the bone. The skin over it was not discolored and not tender.

Roentgenograms showed an irregular configuration of the os calcis, which appeared enlarged, especially on its plantar surface, where an irregularly calcified dense outgrowth was present. The tumor was of a somewhat lobulated appearance and extended mainly along the plantar side of the os calcis in the form of a coarse network of bony trabeculae. There was also some spotted calcification in the plantar soft tissues close to the tumor. The calcaneocuboid joint was practically obliterated.

On the basis of these findings, the diagnosis of osteochondroma of the os calcis was made. Besides the location, the late onset of the growth was unusual (the patient was 27 years old when she first noticed the tumor). As a rule, clinical symptoms of osteochondroma start earlier in life; the active growth of the tumor seems to be intimately related to the process of enchondral ossification of the skeleton and comes commonly to a stop whenever the bone growth of the same stimuli as the cartilaginous cover of the tumor is under the influence stops. It seems that the cartilaginous epiphysal plate, which means that the tumor will show a tendency to grow according to the skeletal growth, but there will rarely be autonomous proliferation. It is rare to observe persistent growth of an osteochondroma after the twentieth year of life, and it is even less frequent to find the tumor developing after this period.

It is hard to assume that the tumor was present since childhood and enlarged after a latent period of so many years. Against such an assumption is the localization in such a highly sensitive region as the heel, in which the smallest tumor formation would readily be noticed. It cannot be entirely denied, of course, that the tumor germ was preformed around the os calcis. A certain fact, however, seems to be that the growth did not become manifest before the twenty-seventh year of life.

Another unusual feature is the frequent recurrence of the tumor, despite eight attempts at surgical removal. As a rule, one succeeds quite easily in the radical removal of a simple osteochondroma. There must have been some particular factor in this case which brought about the peculiar clinical course. First of all, one could be inclined to doubt the correctness of the clinical diagnosis—osteochondroma. To dispel such doubts, a biopsy was performed.

An irregular, nodular tumor was found consisting of cartilaginous and bony tissue and resembling a cauliflower in configuration. Although very irregular, the tumor was sharply outlined against the surrounding tissues, toward which it protruded with nodular cartilaginous formations.



Fig. 2 (case 2).—Osteochondroma of the heel in a woman aged 45. The picture was made after the seventh recurrence of the tumor.

The microscopic examination confirmed the diagnosis of osteochondroma; most of the tissue removed consisted of mature hyaline cartilage well covered by a perichondrium-like dense layer of fibrous tissue. The deeper strata of the hyaline cartilage showed enchondral ossification with the formation of cellular columns and an irregular zone of provisory calcification. The rather porotic spongy bone resulting from this process of enchondral ossification was embedded in hyperemic fatty-fibrous bone marrow. There were no signs of malignancy.

In this case an osteochondroma was being dealt with which was unusual only so far as it showed many nodular cartilaginous prominences on the surface. A lobulated appearance of an osteochondroma is not infrequent; the resemblance to a cauliflower is, however, by no means typical. I think that the abnormal appearance of the tumor was due to the extremely unusual localization. The tight soft tissues on the plantar

side of the feet and the severe pressure effect exercised on this region with weight bearing must modify considerably the cartilaginous tumor growth and change it from a unicentric expansion to a pluricentric growth, depending on the space available and the counterpressure encountered. In adapting itself to the narrowness of the space, which presents itself to invasion, the tumor assumes first a multilobulated and finally a multinodular appearance. It may even be that some of the nodules become detached from the mother growth to form later independent centers of cartilaginous proliferation. (This would explain the roentgenographic presence of the calcified spots in the plantar soft tissues close to the tumor.)

The dispersed tumor particles, and the corrugated relief of the primary tumor make it understandable that radical removal will be difficult. The extension of the tumor permits complete removal only by radical resection of the heel; other less radical procedures are bound to fail from the start. The frequent recurrence in this case was by no means a sign of malignancy; it was due to nothing but inadequate surgical intervention. Every benign tumor, fibroma, lipoma, etc., is likely to recur if not removed entirely. The same is true of an osteochondroma, especially for its cartilaginous component, which represents the actively growing part of the tumor. One can stop the growth of a cartilaginous exostosis by removing the cartilaginous cap. The bony portion, although as a rule making up the greater part of the tumor, is merely the result of the proliferation of cartilage and its subsequent replacement by bone according to enchondral ossification.

It is possible that the localization of the tumor, inducing frequent traumatization by weight bearing and by the shoe, may have stimulated cellular proliferation and thus have rendered the surgical problem even more difficult. After eight failures to eradicate the tumor, the best procedure would be the amputation of the foot. This is preferred to the resection of the os calcis, which is too disabling an operation, and the possibilities of plastic repair are very poor.

*CASE 3.—Multiple cartilaginous exostoses with involvement of the joints.*

A man aged 23 stated that his condition started at the age of 19, when he fell from a horse, on the right side; gradually an enlargement of the right shoulder developed and reached the size of a baseball. It supposedly disappeared under chiropractic treatment. A little later, stiffness appeared in the right hip, with a slowly increasing limp. Also the spine became restricted in motion, and there was pain in the lumbar region and in the shoulders.

On physical examination the patient appeared shortly built (height 4 feet and 11 inches [150 cm.] and weight 112 pounds [50.8 Kg.]) with many palpable exostoses on most of the long bones of the skeleton. The upper extremities showed the characteristic disturbances of growth, with bowing of the radii and shortening of the ulnae. There was marked restriction of motion in both shoulder joints, especially of external rotation, which when tried was very painful.

The right hip joint appeared ankylosed in a position of 20 degrees of abduction, 15 degrees of flexion and 45 degrees of external rotation. A hard bony mass could be palpated in the inguinal region extending downward to the femur. It was very tender on palpation. Huge exostoses were present around the knee joint and on the lower end of the femur as well as on the upper end of the tibia.

The left lower extremity was more than 1 inch (2.5 cm.) shorter, but appeared longer because of the upward tilting of the right half of the pelvis (to compensate for the abduction of the right leg). The left hip joint was markedly restricted in motion, and there were only 45 degrees of flexion, 25 degrees of abduction and 20 degrees of external rotation. The upper end of the femur seemed to be enlarged in the same manner as the right femur.

The spine was without lateral deviation but showed marked rigidity in the sacrolumbar junction and pain on lateral motion.



Fig. 3 (case 3).—Multiple cartilaginous exostoses in a man aged 23. Note the bulbous enlargement of the metaphysis of the humerus with normal joint ends and the pedunculated exostoses of the ribs.

Roentgenograms were taken of all parts of the skeleton. They showed a picture of multiple cartilaginous exostoses, which was unusual because of the enormous enlargement of the metaphysial regions close to the shoulder and the hip joints.

The regions around both shoulders showed essentially the same change. The upper third of the humerus was enlarged and presented an irregular but smooth periosteal surface. There were several bony prominences on the enlarged portion of the humerus. The porotic spongy bone of these exostoses was in direct connection with the bony trabeculae of the diaphysis, which means that the exostoses belonged to the bony structure of the humerus and were not simply superimposed on the periosteal surface. The pronounced, almost diffuse enlargement of the

upper ends of the humerus with the porotic but coarse bony structure suggested that almost the entire upper third had been transformed to an "exostosis," replacing the metaphysis. The upper epiphyses were well developed, the joint surfaces were smooth and there was normal bony structure. On the left side the scar of the epiphysial plate was still visible.

The bones of the forearm showed the more common deformities, such as shortening of the ulnae and bowing of the radii, with exostoses of considerable size along the diaphyses.

Many of the upper ribs showed deformation of the posterior halves, owing to the presence of extensive, irregularly formed exostoses.

The neck of the femur showed tremendous enlargement by an irregular and porotic bony mass, which presented a smooth but uneven periosteal surface and did not extend into the capital and trochanteric epiphyses. The head of the right femur, however, was surrounded by irregular excrescences along its joint margins. The changes were by far more marked on the right side, the bony structure on the left being more dense and homogeneous.

There were other unusual changes in the pelvic bones and in the lumbar portion of the spine. The os pubis was markedly enlarged on both sides but had smooth surfaces. Its bony structure was cloudy and porotic. The configuration of the crest of the right ileum was also irregular where a continuous string of coarse but porotic bony excrescences was found. Both sacro-iliac joints appeared to be solidly fused, and from the upper corner of the right sacro-iliac junction a large densely calcified bony mass extended up to the third lumbar vertebra, firmly uniting these different skeletal portions with each other.

Considerable enlargement of the upper metaphysis of each fibula was also noticed. There were large exostoses at the ends of the femurs and upper ends of the tibiae. These changes were less marked around the ankle joints.

To improve the motion in the right knee joint, an exostosis was removed from the upper end of the tibia. Subtrochanteric osteotomy was performed on the right femur to realine the leg. The patient insisted on a more extensive operation because of the pain and the disability in sitting and dressing. Therefore, the region of the right hip was exposed by a Smith-Petersen incision. The entire upper end of the femur and the adjacent portion of the ileum were the site of extensive proliferation of bone. The cortex was only of eggshell thickness, the bone marrow was red, and there was marked osteoporosis. To expose the head, it was necessary to chisel off huge masses of bone from the trochanter and the neck. The head of the femur appeared normal. The limitation of motion was due to the mechanical obstruction of the joint by the new bony mass. Enough bone was removed to obtain 25 degrees of abduction and 30 degrees of flexion.

This case, although definitely one of multiple cartilaginous exostoses, shows several features which are not typical. As a rule, patients with multiple cartilaginous exostoses become aware of the deformities in childhood and certainly before bone growth stops. In this case there was a relatively late onset of symptoms with increasing severity a long time after the full skeletal growth had been reached. Generally, multiple cartilaginous exostoses cease to grow around the twentieth year of life, when most of the epiphysial plates disappear. They may, of course, persist during the entire life, but clinical symptoms are rarely progressive, and the appearance of new exostoses after skeletal growth has ceased is extremely unusual.



Most of the symptoms of this case were due to the enlargement of the bones close to the big joints of the body, leading to restriction of motion and considerable pain. The pronounced participation of the great joints of the body (shoulder, hip and, to a lesser degree, knee joints) forms an unusual feature in cases of multiple cartilaginous exostoses. In most instances the exostoses form prominences on the diaphyses of the long tubular bones, pointing typically toward the middle of the diaphysis. The bones may become considerably deformed, but more extensive alteration in the motion of the joint does not belong to the typical clinical picture.

In this case the exostoses formed thinly pedunculated bony prominences only exceptionally. They rather involved the entire circumference

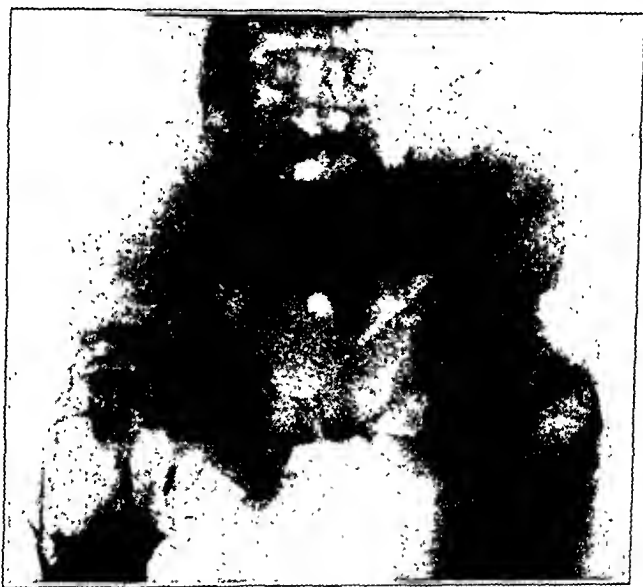


Fig. 4 (case 3).—Enormous enlargement of the metaphyses of both femurs with the heads of normal shape, but interference with motion of the hip joint by a periarticular bony obstacle; enlargement of the ossa pubis and a solid bony mass at the right lumbar region, uniting the lumbar portion of the spine with the pelvis.

of the affected bony portion, thus leading more to the picture of a diffuse hyperostosis than to that of cartilaginous exostoses. The closeness of the bony masses to the joints explains the restriction of motion, despite the fact that the ends of the joints or the epiphyses primarily do not participate in the pathologic process. It seems that the lesion is a purely extra-articular one, mainly metaphysial, and probably due to a disturbed formation of periosteal bone rather than to a lesion of the cartilage of the epiphysial plates. The cartilaginous cover of the metaphysis, which during the first years of life stays in direct continuity with the epiphysial

cartilage and the cartilage of the epiphysial plate, probably does not undergo the normal process of resorption; it may remain preserved to more considerable extent and may later lead, by its proliferation and enchondral ossification, to enlargement of the bony metaphysis, in the form either of a diffuse widening along the entire circumference or of a more typical exostosis, which, however, shows a rather wide bony pedicle.

Such rare cartilaginous exostoses seem to be considered in the literature as intra-articular localizations of the tumors. As I shall point out in the discussion of case 4, this is not correct. In the few cases reported in the literature in which multiple cartilaginous exostoses were complicated by participation of joints there was not a true intra-articular seat of the tumor, but, as in the case just presented, there was such marked enlargement of the juxta-epiphysial portions of the metaphyses that the joints became secondarily involved and the motion of the joints restricted.

The treatment in such cases is indicated by the degree of disability. The mechanical obstruction of the joints by the tumors has to be removed surgically. The operator, however, has to take into consideration the considerable osteoporosis and hyperemia of the tumors when he tries to reduce the bony obstacle.

CASE 4.—*Multiple intra-articular osteochondroma.*

A man aged 26 complained of tumors on the right ankle and knee and stated that as long as he could remember he had had a swelling on the outer side of the right knee and on the outer side of the right ankle. The right leg had grown faster than the left. The mass on the outer side of the ankle had become somewhat larger recently and caused some pain after walking. Changes in weather had no effect. Seven months before the present examination he had a semilunar cartilage removed from the right knee and had been without symptoms since.

Physical examination showed that the right lower extremity was 2 inches (5 cm.) longer than the left. The patient walked with a decided limp to the right, keeping the right leg in abduction. There was atrophy of the calf of  $2\frac{1}{2}$  inches (6.3 cm.). A bony hard tumor mass the size of a walnut, firmly connected to the tibia, could be palpated on the outer side of the right knee joint. There was no tenderness or sign of inflammation. There was a linear scar 6 cm. in length on the outer aspect (removal of semilunar cartilage). Marked grating and pain were noted on extreme flexion. The right ankle was in a varus position. On the outer side, a bony mass the size of half a baseball was present, which was tender to pressure and not movable. The tibio-astragaloid joint had only a few degrees of plantar flexion and dorsiflexion; the subastragaloid joints were stiff.

Roentgenograms of the right knee joint showed considerable deformity of the lateral portion; especially the lateral condyle of the tibia seemed to be deviated toward the joint cavity by a mass of spongy bone which formed a part of the bony epiphysis. The joint surface of the lateral condyle was uneven and showed a dishlike impression. The lateral condyle of the femur showed a corresponding deformity, but to a much lesser degree, which could probably be explained by its

secondary involvement. The outer condyle of the femur was much smaller than the inner. Owing to the marked enlargement of the lateral condyle of the tibia, it seemed that the upper end of the fibula was not normally developed. It remained shorter, and its apex was below the scar of the old epiphysial line, while it was considerably higher on the normal left side. The inner condyles were of normal shape. The anterior compartment of the joint, mainly the suprapatellar pouch, contained from eight to ten joint bodies varying in size from that of a pea to that of a large cherry. They were sharply outlined with irregular and not very dense calcification.

Roentgenograms of the region of the ankle revealed marked deformity of the tibio-astragaloid joint. The astragalus was enlarged by a bony growth on the outer and posterior portion. The growth consisted of coarse bony trabeculation

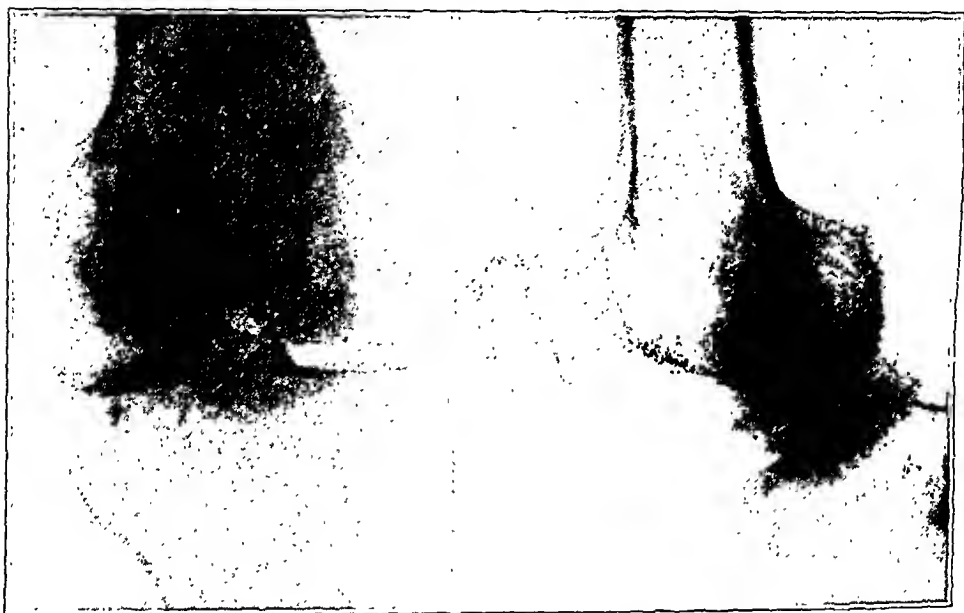


Fig. 5 (case 4).—Multiple intra-articular exostoses in a man aged 26. The anteroposterior and the lateral view of the right knee are shown. Enlargement of the lateral condyle of the tibia, atrophy of the lateral condyle of the femur and joint bodies in the anterior compartment of the knee joint are depicted.

and was connected with the body of the astragalus. Because of the tumor, the entire joint surface of the astragalus became widened, especially in its transverse diameter.

Similar changes had also taken place at the lower end of the tibia. Right above the bony overgrowth of the astragalus the lower end of the tibia showed corresponding enlargement with a bony prominence of relatively dense structure. This prominence surrounded the astragalus from the superior and outer side, forming almost an outer malleolus. The lower end of the fibula was also slightly enlarged and displaced backward, so that the malleolar mortice was practically formed by the lower end of the tibia alone. The inner part of the lower end of the tibia appeared normal. Marginal exostoses of considerable size could also be seen in Chopart's joint and in the anterior portion of the subastragaloid joint, on the scaphoid and the os calcis as well as on the astragalus.

Changes probably of the same nature were also present in both hip joints, being more marked on the left side. The head of the femur was misshaped, and the neck was very short. The bony structure of the inferior portion of the head was irregular, and the joint surface over this area was definitely eroded. The corresponding area of the acetabulum was similarly involved. The changes in the right hip joint occurred mainly in the lower part of the acetabulum, where a small exostosis had formed.

All the other joints of the body were roentgenographically normal.

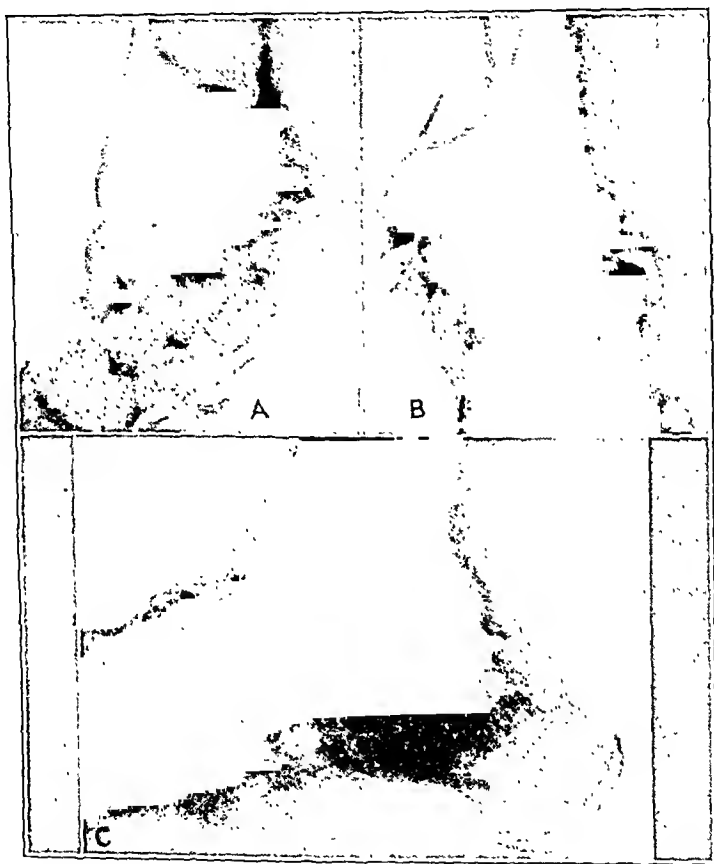


Fig. 6 (case 4).—*A* and *B*, lateral and anteroposterior views of the region of the right ankle. Enormous enlargement of the lateral sides of the tibia and astragalus by huge intra-articular exostoses (osteochondromas) are shown. *C*, lateral view of the region of the ankle after resection of the lower end of the tibia and astragalectomy.

The most striking features were the true lengthening of the right lower extremity for 2 inches and the involvement of several joints of the body (right knee, right ankle joints and left hip joint) by an intra-articular formation of exostoses. Despite the advanced changes in all of the affected joints, clinical symptoms of a marked degree were present only in the region of the ankle. The knee joint, from which the lateral semilunar cartilage had been removed seven months before the patient's admission to the hospital, showed normal

function despite extensive roentgenographic changes. There was not even a disalignment of the joint, although the outer condyle of the tibia was considerably enlarged. One would expect varus deformity of the knee if there were an enlarged outer condyle of the tibia and a normal one of the femur. But the (probably secondary) hypoplasia of the lateral condyle of the femur (mal-development due to pressure effect?) compensated well for the hypertrophy of the tibia, and there was no lateral deviation of the longitudinal axis of the joint, although the transverse axis was broken and run at different levels through the outer and the inner portion of the joint.

This apparently systemic disease of several joints of the body was of longer duration than in the other cases. The patient stated definitely that as long as he could remember the right lower extremity (which showed the main changes) grew faster than the left. There is no reason why the lengthening of 2 inches should not be attributed to the existing changes in the joint, which most likely stimulated the growth in length of the extremity at the site of the affected joint cartilages. I shall discuss this point more extensively later.



Fig. 7 (case 4).—Anteroposterior view of both hip joints. The short neck and irregularly shaped head of the left femur, especially in the inferior portion, are shown.

To liberate the patient from his chief complaint (stiffness and soreness of the right ankle), astragalectomy was performed. The involved anterolateral portion of the tibia and the lower end of the fibula were likewise removed. The foot was set back, the malleolar mortice was remodeled and the collateral ligaments were reconstructed by utilizing the tendons of the posterior tibial and peroneus brevis muscles, and firmly anchoring them in drill canals.

The patient made a good recovery. He was seen again sixteen months after the operation. The foot was in good alinement (fig. 6C). He was walking at least 4 miles every day; the foot never swelled but was sore after he had walked too much. There was still a lengthening of the right lower extremity of 1 inch ( $\frac{1}{2}$  inch in the thigh and  $\frac{1}{2}$  inch in the leg). When both feet were on the ground, the right half of the pelvis was elevated 1 inch. There was slight left convex scoliosis of the dorsolumbar portion of the spine. There was a decided limp on walking, and the right calf was atrophied  $3\frac{1}{2}$  inches (8.9 cm.).

All the specimens removed surgically were studied histologically. A report summarizing the results of a careful study of twenty-six different large areas follows.

On gross inspection there was little similarity between the astragalus of the patient and a normal specimen. The astragalus was heavy and large (3 by 2 by 2 inches [7.6 by 5 by 5 cm.]). On the outer aspect of the body, where one would expect to find the articulating surface with the outer malleolus, there was a huge bony exostosis, which formed a continuous plane with the old joint surface of the body. There was, however, a definite borderline between the old joint surface and the cartilaginous cover of the exostosis. The joint surface of the astragalus was smoothly covered by yellowish white hyaline cartilage of a mature character; the tumor was covered by a rather thin and more primitive cartilaginous layer, which was bluish owing to the underlying hyperemic bone marrow shining through. Several smaller cartilaginous bodies, varying in size from that of a lentil to that of a pea, were noted on the surface of the huge exostosis. The large exostosis appeared definitely as a tumor formation. The smaller exostoses on the head of the astragalus and along the margins of the anterior lower joint surface were more typical of marginal exostoses, such as are frequently found in cases of hypertrophic arthritis. The joint cartilage, however, of the head and of the lower joint surfaces was well preserved. The posterior inferior joint surface appeared to be normal. Examination of the lower end of the tibia revealed a pathologic configuration, mainly due to the presence of a large exostosis at the anterolateral joint border. The osseous part of the tumor was formed by extremely dense spongy bone, with slightly hyperemic bone marrow. At the time of operation some small exostoses could also be observed along the margin of the posterior joint surface of the scaphoid.

On histologic examination the joint cartilage of the upper joint surface of the astragalus showed a normal appearance for the greater extent, with the exception that close to the lateral joint margin some degenerative changes were present, evidently due to mechanical irritation by the intra-articular osteochondroma. The tumor had clearly developed at the joint margin, where under normal conditions the end of the joint is covered only by a layer of synovial or primitive cartilaginous tissue. The tumor consisted of several lobules of irregular porotic and coarse bone tissue covered by a layer of cartilage. The latter had changed from primitive fibrous cartilage to mature hyaline cartilage, the change being dependent evidently on the different localization and the trauma.

At the lateral side, where only the joint capsule touched the cartilage cover of the exostosis, the cartilage was hyaline, with large cell groups in active proliferation surrounded by somewhat watery but basophilic ground substance. The more superficial layers were frequently covered by coagulated fibrin or were impregnated by a fibrinoid substance, as is the rule in soft tissues subjected to frequent mechanical traumatization. Those parts of the intra-articular osteochondroma which were in constant contact with the lower end of the tibia (which was changed essentially in the same way as the astragalus) revealed more pronounced structural changes in their cartilaginous cover. The different degree of pressure exercised on the relatively soft cartilaginous cover of the exostosis evidently accounted for these alterations. The cartilaginous layers were very irregular and showed all the characteristic signs of degeneration as they are encountered in fully developed degenerative (hypertrophic) arthritis. There were huge balls of proliferating cartilaginous cells glued together by hyaline ground substance, which underwent mucoid degeneration in many places. Tears and fissures coming from the surface often separated the cell groups from each other.

Entire tags or spherical portions of the cartilaginous cover could become worn off from the subchondral bone by mechanical friction. The bony tissue of the exostosis, as long as it was protected by cartilage, showed relative osteosclerosis in the subchondral zone. As soon as the protective cartilaginous layer disappeared, the pressure present within the joint cavity surpassed the physiologic degree which stimulates bone growth and developed into a bone-damaging factor, osteoclasia taking place. Below the degenerated cartilaginous cap there was increased resorption of bony tissue, with fibrous bone marrow and cystic formation. More in the periphery, where the pressure ceased, reinforcement of bony trabeculae was taking place by apposition of osteoblastic bone, an osteosclerotic wall of the cyst resulting. The fibrous bone marrow contained many irregular lacunar fragments of bony trabeculae. The entire picture corresponded exactly to the formation of subchondral cysts in cases of hypertrophic arthritis.

Where the cartilaginous layers of the lobules touched each other, there was degeneration of the cartilage of a type, which, to my knowledge, has never been observed in joints before. There was albuminoid degeneration with the appearance of dark blue granules in the cartilage. The cartilaginous cells remained intact and could be found surrounded completely by albuminoid granules. This typical form of degeneration of cartilage is common in the cartilages of the larynx or trachea, and also in the intervertebral disks, but it does not occur in the mature hyaline cartilage of the articulations.

The behavior of the joint cartilage where it bordered at or came in contact with the intra-articular exostosis was of great interest. In part, the joint cartilage was simply overlapped by the exostosis for about 2 cm., and in part the entire thickness of the joint cartilage had become perforated by marrow spaces. These marrow spaces, the result of enchondral ossification of the articular cartilage, brought about a communication between the bone marrow in the subchondral zone of the astragalus and the marrow spaces of the cancellous bone of the intra-articular osteochondroma. On the other hand, the remaining island of joint cartilage formed a good landmark, which showed how much the level of the joint surface had been displaced toward the joint cavity by the new growth. These pictures, as will be seen later, corresponded exactly to the common changes at the joint margins in cases of hypertrophic arthritis.

Where the exostosis overlapped the joint cartilage, a capillary space was to be seen between both cartilaginous layers for almost the entire length. This space made it easy to decide which was the old articular cartilage and which was the cartilaginous cover of the exostosis. The overlapping was mainly due to adaptation of the new growth to the narrowness of the space and to the existing intra-articular pressure. It could be expected that if there were damage to the cartilage by the overlapping, the soft and degenerated cartilage of the exostosis would cede first. As a matter of fact, the cartilaginous cover of the exostosis was very thin along the contact surface with the joint cartilage. It was necrotic in some places, the cells being preserved in the form of shadows, in other places the cartilage was evidently compressed with parallel arrangement of the cartilaginous cells, and in still other places the cartilage had entirely disappeared from the surface of the exostosis. In the latter areas, a secondary connection had taken place between the joint cartilage and the exostosis, with a layer of bony trabeculae lying almost continuously over the joint cartilage. The superficial layers of the joint cartilage took up lime salts wherever they came in contact with the newly formed bone; they remained uncalcified between the bony trabeculae. This

represented an excellent illustrative example of Erdheim's calciprotective law, according to which only those portions of cartilage become calcified which are under static or mechanical stress.

The development of this amalgamation of tissues was probably as follows: The cartilaginous cover of the exostosis, suffering under increased pressure, disappeared completely and became substituted by fibrous tissue from the bone marrow. The fibrous tissue at a later stage of the process formed bony trabeculae along the surface to occlude the open marrow spaces. In some places it even seemed as though the two cartilaginous layers (joint cartilage and the cover of the exostosis) may have fused under pressure similar to the fusion of two metallic substances by heat.

The tissue connection between the exostosis and the joint cartilage may have become interrupted secondarily. A fissure was to be seen running through the

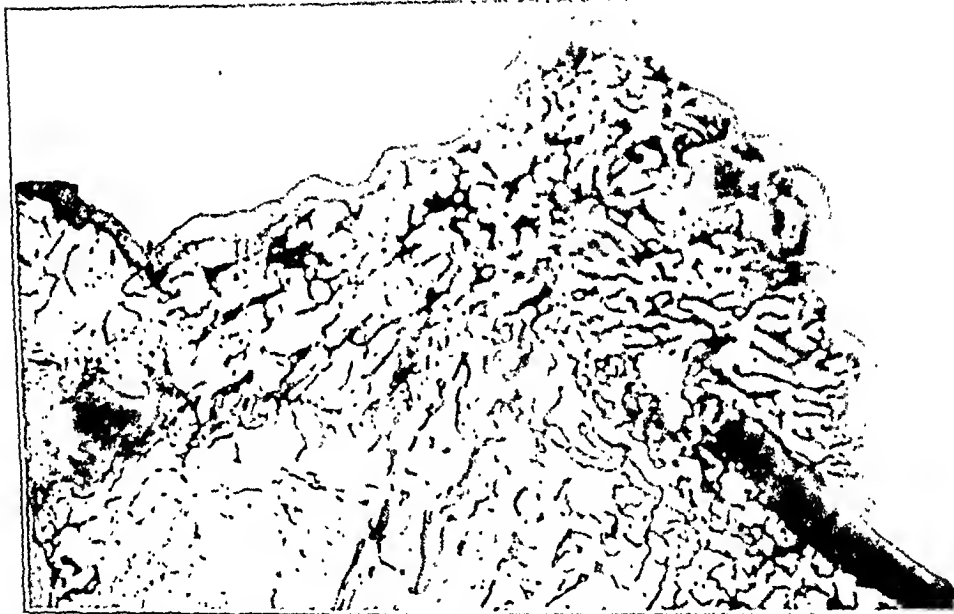


Fig. 8 (case 4).—Low power photomicrograph showing the large exostosis on the lateral side of the astragalus overlapping the joint surface. Several cartilaginous islands are included in the spongiosa, marking the previous level of the astragalus.

superficial layers of the joint cartilage, which had undergone mucoid degeneration. It was certain that some little motion must have occurred between the exostosis and the joint cartilage which was responsible for the localized tissue damaged with increased degeneration and the formation of the fissure.

Where the joint cartilage of the astragalus was overlapped by the exostosis, but only at these doubtlessly traumatized areas, degenerative changes of the old cartilage could be observed similar to the typical cartilage alteration in hypertrophic arthritis.

Close to the joint margin, the zone of provisory calcification enlarged considerably and was perforated in many places by hyperemic marrow spaces. Hand in hand with this increase in calcification of the joint cartilage went a slight



deviation of the cartilaginous-bony junction toward the joint cavity. This was a certain sign that more active enchondral ossification had been going on at the lower surface of the joint cartilage. The aforementioned cartilaginous islands were the remnants of joint cartilage which escaped enchondral ossification when the osteochondroma formed. They showed fully mature hyaline cartilage with many signs of proliferation and mucoid degeneration of the cell groups. They were surrounded on all sides by bony tissue and resembled more rests of the epiphysial plate than of joint cartilage.

The changes at the head of the astragalus and on its antero-inferior joint surface were also of great interest. Here the process was not in such an advanced stage and permitted a better understanding of the earlier stages of this intra-articular tumor formation. It again was clear that the site of the pathologic



Fig. 9 (case 4).—Photomicrograph showing the joint cartilage of the astragalus, separated by a capillary space from the thinned out, partially necrotic cartilaginous cover of the intra-articular osteochondroma. Secondary changes in the joint cartilage (unevenness and accumulation of cells) due to pressure are seen.

process was at the joint margin. Where the joint surface of the head of the astragalus met the anterior joint surface of the subastragaloid joint, a nodular exostosis of the size of a pea was present. It consisted of a spongy bone the marrow spaces of which were in open communication with the cancellous bone of the astragalus. It had a cartilaginous cover which on one side was in direct connection with the articular cartilage of the antero-inferior joint surface of the astragalus and on the other side gradually disappeared toward the head of the astragalus. There remained only a layer of fibrous tissue. Whereas, the joint cartilage of the astragalus was perfectly normal, the cartilaginous cover of the

exostosis was of more primitive, small cellular and proliferative type, with many tears and fissures through the ground substance. The line of separation between these two different cartilaginous layers was rather sharp.

The lower surface of the cartilaginous cover of the small tumor nodules showed a number of marrow spaces, penetrating into the non-calcified cartilaginous layers, but altogether the process of endochondral ossification was not very active, and correspondingly there was a more or less continuous bony lamina separating bone marrow from cartilage (as is the rule whenever endochondral ossification becomes inactive). The bone marrow, even most superficially, was free from hematopoietic elements. This was different from exostoses with more marked growth activity, in which the marrow spaces close to the cartilaginous cover are always hyperemic and rich in cells.

The synovial membrane showed considerable proliferative changes, with many small calcified fragments included in the superficial layers. These inclusions did not impress one as primary bone formation in synovial tissue. They were



Fig. 10 (case 4).—Low power photomicrograph of the distal end of the astragalus. A pea-shaped exostosis between the head of the astragalus and the lower joint surface and small exostoses, not changing the level of the joint surface at the posterior border of the subastragaloid joint, are shown.

most likely small bony particles resorbed from the synovial fluid in which they had been floating after becoming loose from the surface of the intra-articular tumors.

A lesser degree of development than was shown by the osteochondroma on the head of the astragalus was represented by the changes at the posterior border of the subastragaloid joint, where a true exostosis in the sense of a bony prominence at the margin of the joint had not yet appeared. It was very clear from this picture that the intra-articular tumor formation started primarily with the invasion of joint cartilage by marrow spaces from below. At this site, however, the new marrow spaces occupied only the site of joint cartilage; they had not yet expanded to such a degree that the joint level had become altered.

This means that the joint cartilage had become only thinned out from below and replaced in part by bone marrow and spongy bone according to the process of enchondral ossification. But at present there were no signs of a still active enchondral ossification; especially, the zone of proliferation of cartilaginous cells was completely absent. One gained, therefore, the impression that the formation of exostoses came to a standstill relatively soon at the distal portion of the astragalus, whereas exostoses continued to grow at its superior and lateral margins and at the lower end of the tibia.

If one tries to subordinate the changes just described to the better known diseases of the joints, one meets with considerable difficulty. From the histologic point of view, the intra-articular tumor formation



Fig. 11. (case 4).—Medium power photomicrograph of one of the exostoses at the posterior joint border. There are no signs of active enchondral ossification. Slight degenerative changes are seen in the joint cartilage over the exostosis.

had been classified as cartilaginous exostosis or osteochondroma, and there were a number of features in common with hypertrophic arthritis.

The marginal exostoses (frequently, but erroneously called osteophytes) are typical in cases of hypertrophic arthritis. Since Pommer's careful anatomic investigations, it is known that the exostoses in most instances owe their origin to the enchondral ossification of the marginal portions of the joint cartilage, which previously, owing to physiologic wear, trauma, infection, etc., has lost its normal elasticity. The sub-

chondral bone marrow, less protected by the degenerated cartilage, reacts to the increased mechanical irritation with an invasion of the joint cartilage by vessel spaces and vascular and cellular resorption. The resorbed cartilaginous portions are then replaced by bony tissue. This means recuperation of enchondral ossification, which has been quiescent since youth. For some not definitely established reasons (most likely because of the more marked tension stresses within the marginal portions of the articular cartilage), the peripheral parts of the articular cartilages show this "rejuvenescence" of the joint cartilage in the clearest form.



Fig. 12 (case 4).—High power photomicrograph of the border zone between the normal joint cartilage of the subastragaloid joint and the cartilaginous cover to the exostosis. The latter shows many small cartilaginous cells with little tendency to group formation. There are superficial layers with fibrillation and radial fissures, and small cartilaginous nodules in the subchondral bony lamina after herniation of noncalcified joint cartilage through a place of interruption in the zone of provisory calcification and subchondral bony laminae.

with the development occasionally of tumor-like marginal exostoses, resulting from the active process of enchondral ossification. The reactivation of enchondral ossification is the principal cause of the hypertrophy of the ends of the joint in cases of degenerative arthritis.

I do not think that this case is one of hypertrophic arthritis, despite the presence of some of the histologic characteristics of that condition. According to Pommer's functional theory of arthritis deformans, it is the lack of elasticity in the joint cartilage which starts the reactive changes from the side of the bone marrow. The morphologic manifestation of the lack of elasticity is given by degeneration of cartilaginous cells and ground substance. Fibrillation of the superficial cartilaginous layers, fissuring and greater tears can be observed in the noncalcified cartilage together with secondary proliferative cell activity. In case 4 such pictures along the free joint surfaces were absent entirely; on the contrary, the joint cartilage appeared perfectly normal, with the exception of the most marginal portions, where the structural alteration was certainly secondary, owing to the traumatization from the side of the intra-articular tumor. One cannot, therefore, attribute the extensive formation of marginal exostoses in this case simply to hypertrophic arthritis, even to a precocious or juvenile form.

The complete absence of one of the more common causative factors, especially trauma, and the unusually large size of the exostoses on the astragalus and tibia, apart from the histologic picture and the juvenility of the patient, were strong factors against a diagnosis of hypertrophic arthritis. Furthermore, the involvement of the knee joint with participation only of the lateral half of the articulation but without deviation of the longitudinal axis (no primary genu valgum) safely ruled out such a diagnosis.

The term intra-articular osteochondroma could easily induce one to think of the so-called osteochondromatosis of the joints, that peculiar hyperplastic metaplasia of the synovial membrane which may lead to an enormous amount of free and capsular joint bodies. Often in such cases the margins of the joints, with their synovial cover, are especially active sites of the formation of joint bodies. Osteochondromatosis, or better chondromatosis of the joints, however, most commonly affects only one joint and rarely two; in case two joints are found to be affected, they are usually symmetrical, both knee joints for instance. In case 4 there were several joints involved without any symmetry. Moreover, from an anatomic standpoint, there was nothing to suggest primary involvement of the synovial membrane. It did not show any specific alteration at the time of operation, and the histologic picture revealed only non-specific hyperplasia with secondary inclusions of calcified material, but there was no metaplastic cartilage formation, as it is typical for chondromatosis. The presence of a greater number of joint bodies in the knee joint can well be explained by the breaking-off of parts of the intra-articular tumor. I have seen this process of separation of cartilaginous tags in the first stages of the tumor of the astragalus, and it is more than

likely that some of the smaller of these free cartilaginous cell groups may survive in the sufficient nutritive medium of synovial fluid and may even proliferate and calcify, thus leading to the typical picture of free joint bodies.

The best diagnostic assumption in this case is probably that of multiple intra-articular osteochondromas developing on a congenital basis, owing to an error of differentiation at those critical zones of the articulations where cartilaginous and connective tissues meet. All the exostoses had formed right at the joint margins and apparently only in small part on the expanses of the articular cartilage. It seems that the area of transition from cartilaginous to synovial tissue possesses more marked proliferative power than any other portion of the joints. (Some authors [Weichselbaum, Lubosch and others] have even expressed the belief that during the greater part of life the joint cartilage compensates for the daily wear by proliferation of cartilaginous cells at the margins.)

On the basis of such an assumption, the case is considered in relation to the multiple osteochondromas, as they also occur on a congenital (and strictly hereditary) basis. There is, however, a striking difference. In the case reported the seat of the tumor formation was purely intra-articular (the shafts of the bones were perfectly normal); there was an increase in length of the more affected extremity, and there was an increase in the size of the exostoses after skeletal growth had ceased. As a rule, multiple cartilaginous exostoses develop outside of the joint, most likely in connection with the cartilaginous cover of the metaphyses close to the epiphysal plates. (Not all authors agree on the periosteal origin of multiple cartilaginous exostoses, although there seems to be sufficient evidence that in a number of cases cartilaginous islands within the periosteum rather than the cartilage of the epiphysal plates are the primary site of the formation of cartilaginous exostoses.) It is quite conceivable that cartilaginous tumors in earlier life may form at any place around the epiphysis, especially at those cartilaginous parts of the epiphysal cap which later disappear, their place being taken by connective tissue of synovia and periosteum. It would seem that this area (similar to the zones of epithelial transitions, which according to Ribbert are predisposed to the formation of carcinoma) should be inclined to all kinds of errors of differentiation, and one should almost marvel at the rareness of such an occurrence rather than at its existence.

I would say, therefore, that in this case a congenital lesion in the development of joints, a hyperactivity of enchondral ossification at the joint margins, resulting in the formation of marginal exostoses was being dealt with. But a simple error of differentiation at the joint margins does not seem to be sufficient to explain the increase in length

of the right lower extremity and the peculiar deformity of the entire lateral condyle of the tibia. There must be something more than an error of differentiation at the joint margins to clear up the diagnosis.

It is impossible to make the exostoses at joint margins alone responsible for the increased length of the extremity. The right lower extremity remained 1 inch longer even after resection of the lower end of the tibia and after removal of the astragalus. One has to look for a more general cause which could explain the development of the exostoses together with the increase in length. The only possible way to explain both facts is to assume that there was hyperactivity of enchondral ossification around certain joints during the period of physiologic growth in length.

The peculiar picture of the cartilaginous-bony junction at the lower surface of the articular cartilages is nothing but a petrified, extinct process of enchondral ossification. The latter takes place not only at the diaphysial side of the epiphysial plates but also, to a much lesser degree, at the lower surface of the joint cartilages. Here *de potentia* enchondral ossification remains preserved throughout life, whereas at the epiphysial line it is definitely deprived of any further changes to reactivation as soon as the cartilage plate disappears. At the joint cartilages, enchondral ossification may become manifest again under pathologic conditions, for instance in hypertrophic arthritis or, even more, in tabetic arthropathy. This justifies the term "rejuvenescence of joint cartilage" in such conditions.

The value of enchondral ossification of the articular cartilages for the growth of the length of the extremity has been denied by some authors. They have expressed the belief that all the increase in the length of the extremity takes place at the site of the epiphysial plates. However, as enchondral ossification takes place practically only at the diaphysial side of the epiphysial line, it is logical to assume that the bony epiphysis must enlarge by enchondral ossification of the joint cartilage. This means that the lower surface of the joint cartilage is of the same importance for the growth of the epiphysis as the diaphysial side of the epiphysial plate is for the growth of the length of the diaphysis.

One has to figure on a more general disturbance of the enchondral ossification of the joint cartilages than has found its histologic expression in form of the smaller and larger marginal exostoses on the removed specimens. The true lengthening of the right lower extremity for 2 inches suggests more diffuse activity of enchondral ossification, which, if involving the ends of the joint evenly, will, without affecting their shape, lead to an increase in the length of the individual bone and also of the extremity. I am unable to explain why only a relatively small number of joints are affected and why they are affected in an asymmetrical way if the main factor which influences enchondral ossification

is a central one, and it certainly is. Aside from the vague statement of a local predisposition of certain joints, I must admit that the etiology of this peculiar lesion of the joint remains obscure. However, I think that the pathogenesis could be cleared up quite well.

Once the final shape of the ends of the joints was obtained in this last case (around the twentieth year of life), the proliferative activity at the joint margins quieted down with the enchondral ossification, and the small exostoses (in the left hip and right subastragaloid joints) which had developed during the hyperplastic period did not increase in size later. (Histologically, the smaller exostoses were without growth activity; their cartilaginous cover was separated from the bone marrow by an almost continuous bony lamella.) This is another important analogy between the case of intra-articular cartilaginous exostoses reported here and the common cases of multiple osteochondroma. In both instances the exostoses do not represent true tumor formations; they signify merely hyperplastic changes of cartilage. They do not show an unlimited power of proliferation such as one would expect from a true tumor (blastomas); on the contrary, they cease to grow as soon as the skeleton has reached its definite shape, and they may even show regressive changes later in life.

The exostoses in the tibio-astragaloid joint and the enlarged lateral condyle of the tibia, however, do not fit into the category of simple hyperplastic formations. They are real tumors, with active and autonomous growth of their cartilaginous cover. The marked activity of growth is interfered with only by the limited space on the joint cavity. If left unhindered, it is likely that the osteochondroma at the joint margin of the astragalus would assume a similar pedunculated form, such as it often shows in the metaphysial region. Within the joint cavity, surrounded by a tight, nonelastic joint capsule, the tumor has to adapt itself to the narrowness of space, which explains the extensive overlapping of the joint surface.

In summary, I can say that on the basis of a hyperactive enchondral ossification of joint cartilage, true lengthening of an extremity occurred and marginal exostoses developed as simple hyperplastic formations. In a few places, the hyperplastic process went further, to true tumor formation, resulting in huge intra-articular osteochondromas.

The treatment can be symptomatic only as long as nothing is known about the cause of this peculiar disturbance of ossification. In the case reported, the removal of the tumors from the ankle joint by means of astragalectomy was satisfactory. The longer extremity was shortened for 1 inch, and a stable extremity was secured, permitting considerable motion without pain.



# A REVIEW OF UROLOGIC SURGERY

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## KIDNEY

*Anomalies.*—Baker and Colston<sup>1</sup> stated that clinically there is a definite syndrome of symptoms associated with horseshoe kidney. Various indefinite types of abdominal pain may be present, and particularly gastro-intestinal symptoms of varying degree, which are probably correctly attributed to the pressure of the isthmus of the horseshoe kidney on the rich plexuses of splanchnic nerves. The intimate relationship of these nerves to the underlying large vessels makes them particularly vulnerable to pressure exerted from the isthmus. Fusion of the lower poles of the kidneys is the more common type in this anomaly. In a series of 69 reported cases, fusion of the upper pole was found in only 1 case. The anomaly of horseshoe kidney may exist for years without symptoms, and many times it is encountered at necropsy without any clinical record of renal disease in the patient's past history. From a clinical standpoint, the symptoms are usually those of the disease which is present in one or both of the fused kidneys as a result of

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1. Baker, W. W., and Colston, J. A. C.: Surgical Treatment of Horseshoe Kidney with Special Reference to Division of the Isthmus, *J. Urol.* **35**:264-285 (March) 1936.

the anomaly. The diagnosis of the condition is made as a result of investigation which may be undertaken to make a correct diagnosis of the condition of each kidney.

Plastic operation on the ureteropelvic junction of horseshoe kidney, pyelotomy for stones and nephrectomy for tumor, tuberculosis and pyonephrosis have been reported. Foley reported 5 cases in which division or resection of the isthmus of a horseshoe kidney was performed. Symphysiotomy, or division of the isthmus, has been reported in the literature in 24 cases. Seventeen of these were from European clinics. Baker and Colston reported 2 cases in which symphysiotomy was performed. The operative exposure in their cases was through an oblique lumbar incision, which was lengthened anteriorly for a greater distance than in the usual operation on the kidney. Dissection was carried down through muscles and transversalis fascia to Gerota's fascia. Before this structure was opened, it was freed posteriorly to the vertebral bodies, laterally and above as far as the diaphragm. Gerota's fascia was then opened at the level of the posterior lip of the renal sinus, and the perirenal vestments and Gerota's fascia were freed from the kidney by blunt dissection and carried toward the midline. The kidney and its vascular pedicle were thus cleanly and easily exposed. The reflected perirenal fasciae were retracted toward the midline, acting as protection to the peritoneum, and as they were left intact in a single sheath, they were utilized to close the renal fossa after the operative procedure. Exposure of the lower pole and isthmus is the most difficult part of the operation. The small vessels should be ligated and divided, but before any vessel of considerable size is divided, circulation in it should be interrupted for several minutes, and the portion of the kidney which it supplies should be observed to determine the amount of injury to the kidney which would be done by its ligation. After the isthmus has been satisfactorily exposed, in most cases a slight depression and thinning of the tissue will be noted. In some cases the point of union will be found to consist mainly of fibrous tissue with a small amount of renal parenchyma. When the line of division was chosen, the use of a right-angled stomach clamp facilitated exposure and compressed the tissue in such a way as to afford hemostasis while mattress sutures of chromic catgut were being applied. After the sutures were inserted through the kidney on each side of the isthmus, and fat or muscle was applied beneath the stitches to prevent cutting of renal tissue and to facilitate hemostasis, the isthmus was divided by the electrocautery. When the isthmus was satisfactorily divided, bleeding controlled and the right angle clamp removed, the kidneys were allowed to retract. In some cases a second mattress stitch placed through the ends of each stump, with fat and muscle over the raw tissue, may

be advisable. The relation of the pelvis and ureter may then be studied. If a stone is present, the kidney is then so freely mobilized that pyelotomy can be conveniently carried out; or if some indication is present for a plastic operation on the ureteropelvic juncture, or on the pelvis itself, it can be done with the kidney in a more normal position. At this stage it will usually be found that the course of the ureter is not straight, and it is for this reason that nephropexy is an important step in order to insure unobstructed drainage of the pelvis. The kidney should be placed as high as possible in the renal fossa with the lower pole rotated outward. This is best accomplished by two mattress stitches, the first of which is placed opposite the pelvis and carried through the capsule of the kidney, to be brought out above the twelfth rib, and the second of which is placed similarly beneath the true capsule at the lower pole, to be brought out to the lumbar muscles in such a way as to insure lateral axial deflection of the lower calices. Adequate drainage to both stumps should be instituted, and closure of the renal fossa by suture of Gerota's fascia to the quadratus lumborum and sacrospinalis muscles gives reenforcement to the nephropexy.

Gutierrez<sup>2</sup> stated that congenital anomalies are more commonly observed in the urinary tract than in any other system of the body and that fully 40 per cent of all pathologic conditions of the kidneys and ureters are due to malformations. The introduction of modern methods of urologic examination, and especially of pyelography and intravenous urography, has made it possible to diagnose preoperatively innumerable common malformations of this tract, the existence of which was formerly discovered only at operation or necropsy.

The various types of anomalies of the upper part of the urinary tract have been carefully classified anatomically and clinicopathologically in three tables, where they are systematized according to whether they concern the number, size, form and position of the kidney proper, its excretory apparatus or its blood and lymphatic supply.

The part played by these anomalies is by no means confined to diseases of the urinary tract alone. It is obvious that ectopia of the kidneys or ureters, abnormalities of contour, size or number, fusions, false openings of ureters and anomalous position of renal blood vessels or lymphatics may work havoc not only within the urinary system but also at points remote from the kidneys and ureters, giving rise to obscure abdominal or pelvic symptoms that are readily suggestive of lesions of organs within the gastro-intestinal or genital tract. These symptoms, which may even be wholly silent as regards the urinary tract, or in which urinary symptoms are only of a minor nature, are to

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2. Gutierrez, Robert: *Rôle of Anomalies of Kidney and Ureter in Causation of Surgical Conditions*, J. A. M. A. 106:183-189 (Jan. 18) 1936.

be attributed for the most part to pressure or traction exerted on other organs or nerve plexuses by the abnormal kidney or ureter. Often the patient has been subjected to one or more abdominal operations without relief before he is referred to the urologist. It is therefore of great importance in every case in which the slightest urinary symptoms have become manifest that a careful cystoscopic and urographic study be made, for experience has shown that such a study often reveals a congenital abnormality of the kidney or ureter as the underlying cause of the entire syndrome. In some cases of hypoplastic or aplastic kidney there may be an entire absence of urinary symptoms and a history of bilateral abdominal pain, or there may be lumbar pain and symptoms of chronic nephritis. Even in cases of hydronephrosis, symptoms of gastro-intestinal disturbance may predominate, or tumor formation may be the only symptom. In other cases there may be only slight frequency or dysuria, while in still others there may be severe renal colic and vesical tenesmus, accompanied by chronic cystitis or pyelitis.

It has been demonstrated that any such congenital anomaly is likely eventually to require surgical intervention, since it predisposes to poor function and to urinary stasis, with resultant retention and possible infection. In many cases of chronic pyuria and recurrent attacks of pyelitis or nephritis in children, the underlying cause has been found to be a malformation of the upper part of the urinary tract. Deficient function, nephritis and pyelonephritis, as well as hydronephrosis and calculus, are common in kidneys that are congenitally abnormal; and in cases in which only one kidney reveals an anomaly, the opposite kidney, although normally developed, may suffer from the additional strain imposed on it. Fused kidneys of various type, and especially horseshoe kidneys, are usually associated with some degree of ectopia and with abnormalities in the renal pelvis and in the form or number of the ureters. Hence they are frequently the site of pathologic lesions.

One of the most characteristic clinical syndromes is that which is associated with horseshoe kidney, in which there are always anomalies of the pelves, ureters and blood vessels. The three main clinical features of this syndrome are: (1) abdominal pain in the epigastric or umbilical region, (2) a history of chronic constipation with or without gastro-intestinal disorders and (3) urinary disturbances with early signs of chronic nephritis. Since frequently in the early stages the abdominal symptoms may predominate, a considerable period of time may elapse before the patient comes to the urologist. The abdominal symptoms are due to the fixation of the horseshoe kidney and the abnormal pressure it causes on the surrounding organs, nerves and blood vessels. The urinary symptoms are due fundamentally to lack of renal drainage,

cent) revealed the presence of caliectasis, pelviectasis or ureterectasis alone or in combination. In 19 of these the dilatation was of grade 2; in 4, of grade 3, and in 3, of grade 4.

The results after operation by the method of Woodruff and Scherer were as follows: Six (9.2 per cent) of the patients could not be traced; 55 (93 per cent) patients were completely relieved; 3 (5.3 per cent) had been definitely helped, and 1 patient (1.7 per cent) was not relieved by operation. Of the 65 patients, 48 (74 per cent) had pyelograms or excretory urograms made at varying periods after operation. The kidneys of the 48 patients were maintained in excellent position, i. e., the position in which each was fixed at operation.

Birdsall<sup>5</sup> found that the operation described by Kelly and Brodel was the most satisfactory for anchoring the kidney in its correct anatomic position. Three sets of triple mattress sutures of no. 1 chromic catgut are introduced through the capsule on the posterior surface of the kidney, the upper set being inserted through the capsule of the upper pole of the kidney and the second and third sets through the capsule of the middle and lower poles, respectively. The kidney is then placed in its new bed, its proper position is determined and the fixation sutures are introduced so as to maintain this object. It is essential to place the kidney so that free drainage is accomplished, and this can be done by fixation of the upper pole of the kidney at a point closer to the spine than the lower pole. The upper sutures are, in most instances, brought through the intercostal muscle between the eleventh and the twelfth rib; the second and third sets of sutures are introduced immediately below the twelfth rib and through the erector spinae muscles. The introduction of the fixation sutures is best accomplished by the use of a long, curved Reverdin needle. By this technic, the kidney is fixed in as high and correct an anatomic position as it is possible to obtain; its posterior surface is in direct contact with the lumbar muscles, and there is no possibility of rotation, as is the case when its convexity is sutured to the edges of the incision.

By this method of suspension, nephropexy was performed by Birdsall in 57 cases of unilateral and in 9 cases of bilateral nephroptosis, making a total of 75 kidneys suspended. The end-results obtained were excellent in 73 kidneys. In 2 kidneys the operation failed; in 1 of these the technic in the introduction of the sutures was faulty, and in the other marked hydronephrosis was present. This kidney became infected, pyelonephritis developed and nephrectomy was necessary. Pyelograms, made with the patient in the erect position, after nephropexy, have been taken of 26 kidneys, and in each case the position of

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5. Birdsall, J. C.: *The Symptomatology, Renal Pathology, and Treatment of Nephroptosis*, J. Urol. **35**:135-155 (Feb.) 1936.

the kidney was excellent, and there was no apparent advancement of renal destruction. After nephropexy it is essential that the patient be kept in bed in the recumbent position long enough for firm adhesion to form and hold the kidney securely in place in its new and permanent situation. The patient is kept in the dorsal position the first week, but may be turned on the side on which operation was performed the second week and allowed to sit up in bed at the end of the fourth week. Many patients complain of vague pains and regions of anesthesia for several months after the operation. An abdominal support is not necessary.

**Tumors.**—Pohle and Ritchie<sup>6</sup> reported 6 cases of malignant tumor of the kidney in children. The mixed tumor occurs chiefly in children usually less than 10 years of age, though it is sometimes found in adults. It not infrequently occurs bilaterally and may be found in any part of the kidney. The size varies with the age of the growth at the time of its discovery. The tissue of the tumor is usually sharply demarcated but may be infiltrative. The gross structure is extremely variable and may include hemorrhage, necrosis and cartilage or the formation of bone as special features.

Tumor of the kidney in children generally does not produce symptoms until the growth has reached considerable size. In contrast to hypernephroma, this highly malignant neoplasm seldom causes hematuria early in its course, and the absence of pain also tends to prevent its early discovery.

The diagnosis of a fully developed tumor of the kidney in a child is usually not difficult. In the differential diagnosis, pyelography and intravenous urography are important aids. If sufficient tissue of the kidney has been destroyed, the involved side is not visualized after the intravenous injection of the dye.

The prognosis of tumor of the kidney in children is unfavorable. Although occasionally a patient may survive, the available data indicate that the mortality is more than 90 per cent. In 17 of a total of 163 cases of neoplasm of the kidney the growth was classified as Wilms' tumor; only 1 of the 17 patients survived operation by a few years.

Before the advent of high voltage roentgen therapy, the treatment of tumor of the kidney in children was entirely surgical. Since such a tumor is composed largely of embryonic tissue, it may be assumed that it is radiosensitive. Marked reduction in size may be brought about by roentgen therapy. As soon as the tumor has been reduced to such an extent that it is barely palpable and provided the general condition of the patient is satisfactory, removal of what remains of the tumor may be attempted. The technic of treatment is simple. Usually

6. Pohle, E. A., and Ritchie, G.: Malignant Tumors of the Kidney in Children, with a Report of Six Cases, *Radiology* 24:193-203 (Feb.) 1935.

exposure of one anterior and one posterior field suffices; if the tumor is large, a third lateral field can be exposed. The question of dosage is a matter of debate. Even with relatively small doses, violent systemic reactions, sufficiently severe to force interruption of the treatment, occurred. The poor general condition of the patient, when the blood count is low, also renders moderate or small doses advisable. If pain is severe, roentgen treatment may be palliative and is therefore indicated. Treatment of metastatic lesions in the lungs is not recommended, although, theoretically, they should respond because of the radiosensitivity of the primary tumor.

An analysis of these 6 cases of tumor of the kidney revealed a high degree of malignancy. Operation alone or combined with irradiation seemed ineffectual in eradicating the disease. A striking temporary improvement was followed soon by either a local recurrence or widespread metastasis, which led to death. The lungs seemed to be the most frequent site of secondary involvement.

It has been observed that a tumor may almost completely disappear after roentgen therapy, so that palpation will not definitely reveal any mass in the region of the kidney, but laparotomy often reveals the presence of a moderately large residual tumor. In the authors' experience, preoperative irradiation did not in any way complicate the surgical procedure. It was an unexplainable fact that the only surviving patient had received roentgen treatment solely; the tumor was not removed, nor was nephrectomy performed. In spite of this case, Pohle and Ritchie expressed the belief that preoperative irradiation and removal of the residual neoplasm, followed by postoperative irradiation, are the most satisfactory method of treatment.

According to Braasch and Griffin,<sup>7</sup> carcinoma of the renal cortex may be divided into two types which have distinct clinical characteristics, namely, adenocarcinoma (hypernephroma) and alveolar carcinoma. Metastasis occurs most frequently with renal tumors of the higher grades of malignancy and may be present without causing clinical evidence. Lymphatic extension occurs frequently. Metastasis is found most often in the lungs and rarely in the osseous system. Although the progress of the disease in the presence of pulmonary metastasis may be delayed by nephrectomy and irradiation of the lungs, postoperative results indicate that the chance for recovery is so slight that operation is not justified. Calcification of tissues in cases of renal adenocarcinoma is a frequent occurrence and indicates a favorable

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7. Braasch, W. F., and Griffin, Miles: The Prognosis in Renal Carcinoma and the Clinical and Pathologic Data Affecting It, *J. A. M. A.* **106**:1343-1346 (April 18) 1936.

prognosis. Urographic evidence of widespread involvement of all calices and of the pelvis indicates a high grade of malignancy and a guarded prognosis.

Although clinical data suggest that adrenal elements may be included in some hypernephromas to account for the vascular manifestations, such as hypertension and telangiectasis, neither chemical analysis of the tumors nor postoperative clinical data corroborate such an assumption. Although the size of the tumor alone has no bearing on the late postoperative results, a large, fixed tumor, together with a history of short duration and evidence of marked toxemia, indicate that the prognosis is unfavorable and that the advisability of operation is questionable.

Bond<sup>8</sup> reported that in 176 cases of carcinoma of the genito-urinary tract in which treatment was given, complete follow-up data were available in 156 (90 per cent). Only cases in which the existence of carcinoma was definitely proved microscopically are included in the computation of results. Fifty-one cases in which the diagnosis clinically was carcinoma were rejected because microscopic material was not available. The number of proved cases considered in this report is 118. There were 14 cases of renal tumor. In 5 of these the growth was an adenocarcinoma with granular cells and in 5 a papillary carcinoma with clear cells. In 12 of the 14 cases hematuria was the main symptom. The duration of the hematuria varied from four days to eight years before the patient was examined. The epidermoid carcinoma was associated with renal calculi; the duration of life after nephrectomy was eighteen months. Death was due to extensive local recurrence. The treatment in all cases was nephrectomy. Roentgen rays and radium were used in only 1 case. Six patients (43 per cent) lived five or more years after treatment. One patient was alive and well twelve years after treatment; 1, ten years; 1, nine years, and 1, five years. One lived nine years and died from pneumonia; another lived six years and died from the same cause.

There were 63 proved cases of carcinoma of the bladder. This was after exclusion of 28 cases which were rejected because of insufficient microscopic data. In 45 per cent of the cases of carcinoma of the bladder the growth was of the epidermoid type; in 29 per cent, it was a papillary carcinoma and in 16 per cent, an adenocarcinoma; in the remaining 10 per cent, the growth was a scirrhous, medullary or cellular carcinoma of undetermined histologic type. In 47 cases (76 per cent) the chief symptom was hematuria. According to the patients' statements, this had been present for from eight days to twenty-five years.

8. Bond, F. T.: Experiences with Renal and Vesical Carcinoma, *J. Urol.* 35:309-315 (March) 1936.



In 7 cases the bleeding had existed for more than six years. The treatment in these cases was undertaken with the intention of resection or excision if such a procedure was physically possible. In practice, the tumor usually was so extensive, involving the ureter and trigon, that resection was possible only in 6 cases and excision in 6 others. In 24 cases the treatment consisted of cystotomy, fulguration of the tumor and implantation of radon seeds. The results of treatment follow: Seven patients (11 per cent) lived five years or longer; 2 patients were alive and well after eleven years, 1 patient after eight, 1 after seven and 1 after five; 1 patient lived ten years and another seven years, and neither died from carcinoma.

Counseller and Menville<sup>9</sup> stated that benign tumor of the kidney is extremely rare, and even when present, it seldom gives rise to symptoms which necessitate surgical intervention. Among the benign growths which have been encountered in the kidney are adenoma, lipoma, fibroma, myxoma, myoma, hemangioma, lymphangioma and chondroma. The authors present a case in which nephrectomy was required because of two benign lesions in the lower pole of a kidney that also had duplicate pelves. A woman aged 29 noticed a painful tumor in her left flank six months prior to examination. Mild frequency, dysuria and hematuria had occurred. Roentgenographic studies of the left kidney showed marked deformity characterized by upward and medial displacement of the pelvis, flattening and obliteration of the lower calices and flattening of the lower border of the pelvis. The lesion was thought to be a cyst or a tumor. The right kidney was normal. At the time of operation a large cystic mass was found in the lower pole of the kidney. The cyst was opened and evacuated, and an irregular mass suggestive of a malignant growth was found at its base. Nephrectomy was performed. Pathologic study of the kidney revealed a large cyst of the lower pole containing a mass of spongy tissue with the histologic characteristics of leiomyoma. Because of the proximity of the tumor to the pelvis and calices, it was thought that it might have originated in the smooth muscle of a calix or of the pelvis. No evidence of malignancy was noted.

*Stone.*—Cifuentes<sup>10</sup> stated that bilateral reno-ureteral lithiasis occurs more frequently than is generally believed; it affects about 20 per cent of the patients with renal lithiasis. This is because the intrinsic disease (diathesis, metabolic disturbances, etc.) does not act at random

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9. Counseller, V. S., and Menville, J. G.: *Leiomyoma Associated with Benign Cysts in a Kidney with Duplicate Pelves*, *J. Urol.* **35**:253-258 (March) 1936.

10. Cifuentes, Pedro: *La litiasis reno-ureteral bilateral (Estudio clínico e indicaciones en su tratamiento)*, Madrid, Grafica Universal, 1935.

on one kidney alone but affects the two kidneys, both of which are subjected to the same disturbances and in an identical way.

In most cases the evolution of the disease runs a latent course in one or in both kidneys, and the calculi reach a considerable size before symptoms appear; pyuria is often the only clinical manifestation until roentgenographic examination reveals that the condition is bilateral.

When operation is performed it should be done in two sittings, one or two months apart. Generally speaking, the kidney that is least affected should be the first operated on, the stone being removed by simple pyelotomy. This insures improved function of one kidney and permits greater freedom in surgical intervention on the other kidney at a later time. If, however, the condition of the more seriously impaired kidney constitutes a danger to life, this kidney should be the first one operated on, treatment of the sounder kidney being left until later. If there is a ureteral stone on one side, this side should be operated on at the outset, to overcome the danger of a sudden blockade of the ureter. If calculi are present in both ureters, an attempt should be made to remove them by ureteral catheterization when their size permits. If this is impossible, ureterotomy should be done first on the side that has more recently been obstructed, provided the stone on the other side is well tolerated.

The presence of renal insufficiency revealed by functional tests is not an absolute contraindication to operation; it may be possible by suitable urologic treatment to improve the function and to save at least one kidney.

In treating bilateral lithiasis, three fundamental principles should be observed: 1. Abstention from operation, in the presence of evident contraindication, in many cases in which tolerance has been established will enable a patient to survive for a long time. Under such conditions, only the occurrence of a grave, acute accident should lead the surgeon to perform an emergency operation. 2. In a substantial number of cases operation should be done on one side only, to conserve a kidney that guarantees good function, with abstention from operation on the other kidney in cases in which this has attained a certain degree of tolerance and in which intervention might mean a risk for the patient. 3. Nephrectomy should be resorted to in cases of bilateral lithiasis only in exceptional instances.

Not infrequently lithiasis appears in the second kidney after the condition has been observed or after operation has been performed on the assumption that the disease was unilateral. This occurred in 13 per cent of the author's cases. This is one of the most tragic situations that may occur in pathologic changes in the urinary tract because of the anuria that appears on the occasion of the slightest nephritic colic

and for which ureteral catheterization, ureterotomy or nephrotomy must be promptly performed. For this reason one may well hesitate to perform nephrectomy if a stone is present in one kidney.

As recurrence frequently occurs after conservative procedures, the opposite kidney should not be removed even for severe infection or extensive calculosis unless it is certain that the other kidney has been completely cured and that further stones are unlikely to develop.

Anuria in a patient with lithiasis, even when he presents a syndrome affecting only one side, should make the urologist regard the lithiasis as really bilateral. This is why it is always an extremely grave symptom, for which ureteral catheterization should be done without delay and nephrostomy carried out while there is still hope for its success.

Counseller and Hoerner<sup>11</sup> stated that nephrostomy is a surgical procedure that has been in use for many years, but only comparatively recently have advances been made which have widened its field of applicability. A review of 209 cases of large or multiple renal stones in which operation was performed from 1929 to 1933, inclusive, is presented. This period was selected because it coincided with the time that nephrostomy began to be more frequently employed at the Mayo Clinic in the treatment of these conditions. A diagnosis of unilateral stone was made in 164 cases and of bilateral stones in 45. Of the 45 patients with stone in both kidneys, 21 underwent bilateral and 24 unilateral operation. In some of the cases in which the condition was bilateral, operation was performed on one side only because the stones in the other kidney were less than 5 mm. in diameter and complications were not present.

Simple pelviolithotomy often gives satisfactory results in the presence of large renal calculi. In such cases renal function returns rapidly subsequent to the release of the obstruction. In some cases it is frequently difficult to determine whether adequate drainage will be obtained without nephrostomy. One of the chief indications for nephrostomy is in calculous anuria, in which case it is necessary to establish temporary diversion of the urine. The obstruction may be relieved at the same time, provided the condition of the patient warrants it. Nephrostomy may also be advisable in the presence of chronic, partial obstruction that has produced a variable amount of injury to renal tissue. Although infection cannot be demonstrated in some of these cases before operation, not infrequently it becomes a serious complication after operation. It is possible in such cases that operation may have stirred up a latent process or that contamination occurred at the time

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11. Counseller, V. S., and Hoerner, M. T.: *An Analysis of the Effectiveness of Nephrostomy in the Treatment of Large Renal Calculi*, J. Urol. **35**:21-31 (Jan.) 1936.

of the surgical procedure. Under the circumstances, nephrostomy promotes a smoother convalescence by providing better drainage. When infection is known to exist in conjunction with chronic obstruction, the function of such kidneys is always uncertain, as present diagnostic aids under these conditions are not reliable. Not infrequently an apparently functionless kidney will be found at operation to contain a considerable amount of valuable renal tissue. Proper drainage by nephrostomy facilitates the eradication of the infection and the return of function of the remaining renal tissue to its full capacity. There is another type of renal lithiasis in which large stones fill both pelves and are not removable by present surgical methods. Although these calculi may produce no symptoms, they gradually destroy renal tissue and eventually lead to a fatal outcome. Nephrostomy will maintain satisfactory renal function for years in such cases.

Permanent nephrostomy is reserved for cases in which the underlying pathologic condition cannot be remedied satisfactorily. Drainage by temporary nephrostomy is maintained for a variable period, depending on the condition of the kidney at operation and subsequent evidence of improved function and diminished infection.

Nephrostomy has several significant advantages over pyelostomy. Retention of a catheter in the pelvis of the kidney for more than one or two weeks after pyelostomy is difficult, and when it is necessary to change the tube because it has become obstructed by débris, replacement of the catheter is often troublesome and sometimes impossible. Drainage through the cortex is more effective than through the pelvis, for a catheter in the pelvis may prolong the irritation of the mucous membrane. There is probably less tendency to this with nephrostomy. Pyelostomy is favored by some surgeons because it does not destroy renal tissue. Nephrostomy can be done with little injury to renal tissue, and the catheter can often be placed in the wound through which the stone was removed. One of the important advantages of nephrostomy is the fact that there is much less danger of renal fistula.

Fifty-nine cases in which nephrostomy had been performed and 86 cases in which it had not were compared as to results. Improvement of the original pathologic condition was noted in 48 per cent of the cases in which nephrostomy was performed but in only 25 per cent of the cases in the other group. There was a negligible and insignificant difference in favor of the group in which nephrostomy was not performed in regard to recurrent stones and improvement of hydro-nephrosis and in the pathologic condition of the kidney. Subsequently, nephrectomy was required in 6.8 per cent of the cases in the group in which nephrostomy was performed and in 1.2 per cent of the other group. It was noted that the original pathologic condition was definitely more serious in the group in which nephrostomy had been performed.

## TUBERCULOSIS

Papin, Goidin and Busser<sup>12</sup> pointed out that the pathogenesis of the caseous form of renal tuberculosis is always obscure and that it has never been possible to reproduce it experimentally. Attempts to do so have always resulted in the granular form. While it appears indisputable that the invasion of the kidney has taken place by way of the blood stream, it is impossible to explain why the lesions assume a special character in the forms which have with more or less reason been called "surgical tuberculosis of the kidney." A lymphatic theory of their origin does not account any better for the fact that renal tuberculosis begins in the medullary portion of the kidney.

As an aid in clarifying the pathogenesis of caseous tuberculosis of the kidney, the authors presented a case in which the lymphatic origin of the lesions seems beyond dispute. When the left kidney, which had been removed, was examined, three small well defined nodules, each about 1.5 cm. in diameter, were observed at the ischemic upper pole, literally within the lips of the hilus and at its base, flush with the intrahilar fat and slightly encroaching on the adjacent renal parenchyma. Histologic examination revealed that all three were typical tuberculous nodules, caseated at the center and bordered by a layer of epithelioid and lymphoid cells. Although the nodules were adherent over a small amount of surface to the renal parenchyma, which was more or less infiltrated by granulation tissue, the greater part of each one was surrounded by the hilar fat, which was likewise infiltrated with inflammatory elements. On one of them, near the axis of a blood vessel, was a small aberrant group of tuberculous follicles and also a center of caseation which had reached and surrounded the wall of a fair-sized artery, causing the musculo-elastic layer to undergo caseation with more or less tendency of the lumen to become obliterated. Adjacent to another of the nodules there was a small lymph node crowded with tuberculous follicles. Small amounts of inflammatory infiltrates were found moderately disseminated through the renal parenchyma, generally near the vessels, and there was ischemic necrosis of almost all the cortical zone contiguous to the tuberculous nodules. No tuberculous follicles were found at any distance from these nodules beyond the small mass.

The ensemble of lesions is suggestive, not so much of common renal tuberculosis as of tuberculous adenopathy of the hilus, with invasion of the renal tissue from the lips of the hilus, associated with secondary vascular lesions which had led to ischemia of the cortex through obliteration of the lumen of the artery. It was this rather unusual mechanism of production that led the authors to report the case.

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12. Papin, E.; Goidin and Busser: *Tuberculose rénale secondaire à une adénopathie tuberculeuse hilaire*, Arch. d. mal. d. reins 9:197-203 (March) 1935.

Pugh,<sup>13</sup> in a review of cases of tuberculosis of the kidney in pregnant women, noted that abortion or nephrectomy was practiced in about 70 per cent of cases in which exacerbation of unilateral tuberculosis occurred during gestation. These facts suggest that conservative measures are definitely contraindicated. As the renal process is acutely exacerbated in practically all cases of obstruction, immediate intervention is urged. Interruption of the pregnancy fails to check the process of the disease and is dangerous, particularly in the later months. This procedure should be resorted to only when the patient refuses nephrectomy or when infection of both kidneys is present.

From the evidence reviewed the conclusion may be drawn that pregnant women stand the operation of nephrectomy particularly well; in fact, it seems no more serious than when attempted on women who are not pregnant. All of 18 patients on whom nephrectomy was performed recovered. In 5 cases in which operation was not performed the condition was serious; in 2, death occurred late in pregnancy. It is a well recognized fact that children of tuberculous parents are particularly susceptible to infection by the bacillus of tuberculosis, not by placental transmission but because they are good culture mediums. Stevens,<sup>14</sup> quoting Morris, stated that the average mortality is approximately 60 per cent among children born of tuberculous mothers. It is therefore to the advantage of both mother and child to proceed with early removal of the tuberculous focus of infection. Matthews, in 1921, in a study from the literature of 265 pregnant women on whom nephrectomy was performed, found that labor of 200 was normal and of 15 complicated, with 2 deaths.

*Schistosomiasis.*—Stevens<sup>14</sup> reported a case of infection of the upper part of the urinary tract with *Schistosomum*. This was a rare case of renal involvement and was unusual because the lesion was a papillary growth of the pelvis and calices, which in this case seemed to have been the primary involvement of the urinary tract. The left kidney, which was eroded, together with about 7 cm. of ureter, was removed intact extraperitoneally. The ureter was split open, and a pedunculated papilloma more than 1 cm. in diameter was found about 4 cm. from the pelvis. The latter was largely filled with a papillomatous growth. Later the kidney was sectioned, and similar growths were found widely scattered over the walls of the hydronephrotic sac. The pathologic diagnosis was papillary epithelioma of the pelvis of the kidney, but

13. Pugh, W. S.: Tuberculosis of the Kidney in Pregnancy, *J. Urol.* **35**:160-171 (Feb.) 1936.

14. Stevens, A. R.: Schistosomiasis Involvement of the Upper Urinary Tract: Report of Patient with Papillomata of Renal Pelvis, Ureter, and Later of Bladder, *Tr. Am. A. Genito-Urin. Surgeons* **28**:275-283, 1935.

the gland gave evidence only of lymphoid hyperplasia, with no evidence of metastasis. Convalescence of the patient was uneventful. Later the remaining part of the left ureter was removed with the adjacent wall of the bladder, and a portion of the bladder containing the group of small papillomas was resected. Histologic examination of the tumors of the ureter and bladder revealed a papillary growth in association with which were numerous ova, some of which presented a terminal spine. A restudy of the tumors of the kidney was then made, and in one section a definite ovum was found. The patient made an uneventful recovery.

Hager<sup>15</sup> stated that schistosomiasis is a general term which implies an infection with any of the blood flukes or trematodes, of which there are three species that are pathogenic for man, namely, *Schistosomum japonicum*, *Schistosomum Mansoni* and *Schistosomum haematobium*. They differ primarily in their geographic distribution, in their selective localization within the human host, in their requirement of a specific mollusk for their intermediary metamorphosis and in their respective ova. *S. japonicum* is the oriental genus, confined mainly to Japan and China. It causes symptoms in the lungs and liver. The bladder never becomes involved; so it is of no particular concern to the urologist. *S. Mansoni* and *S. haematobium* are both common to Africa, where schistosomiasis is widespread in many sections. *S. Mansoni* exists in the western hemisphere. It may be regarded as a heritage from the slaves and it has remained limited to the West Indies and certain localities in South America where conditions favorable for the completion of its life cycle obtain. The presence of the necessary intermediary host, therefore, limits the geographic distribution of the disease. Although certain laboratory animals have been infected experimentally, there is no evidence to show that they become infected in their natural state. *S. Mansoni* has a predilection for the rectum and is characterized by rectal lesions. In Africa, where both forms of *Schistosomum* are prevalent, a double infection may occur in which infection with *S. Mansoni* occurs in the bladder as well as in the rectum. In the West Indies, where infection with *S. Mansoni* alone occurs, the bladder does not become involved.

Vesical schistosomiasis or bilharziasis is characterized by lesions of the urogenital tract, usually of the bladder. Two features in the diagnosis are particularly emphasized by Hager. The first is the use of an extract of cercariae for a cutaneous test. The second is the value of a roentgenogram in the recognition of vesical schistosomiasis. Myriads

15. Hager, B. H., in discussion on Stevens.<sup>14</sup>

of ova are expelled into the lumen of the bladder and are passed with the urine. However, not all of them are extruded into the bladder, as many of them become arrested in the submucosa, where they undergo calcification. The calcified ova in the tissue cast a characteristic shadow on the roentgenogram which is pathognomonic of bilharziasis. In bladders in which the process has been extensive, there is a vague opacity that more or less outlines the periphery of the bladder which might be compared to the shadow cast by a fetal head. When calcification in the lower part of the ureter is marked, a mottled shadow of the dilated ureter can be demonstrated. Intravenous urography is particularly useful in the demonstration of obstructive uropathy, because of the difficulty of instrumentation incident to the distortion and formation of fistula in the urethra. Antimony and potassium tartrate is a specific for the disease. It kills the parasite, and it also destroys the eggs which have been deposited in the tissue. Christopherson, who introduced this drug, suggested a course of 30 grains (2 Gm.) given in solution intravenously over a period of from twenty-eight to thirty days.

*Cysts.*—Lindenfeld,<sup>16</sup> in a study of solitary cyst of the kidney, found reports of only 257 cases recorded in the literature, from which it must be concluded that the condition is rare. Since 1931, 5 cases have been recorded in his clinic in Krakow, on which he has based his article. Every cystic formation in more or less intimate contact with the kidney or its integuments is a cyst of the kidney, regardless of its histologic picture, the establishment of its renal structure or the presence of an epithelial lining. The sole criterion which shows that it belongs to the kidney is its localization, according to Lindenfeld.

Classifications of solitary cysts of the kidney have had little uniformity and many contradictions. Lindenfeld adopts the classification of Israel, with slight modifications, as follows: (1) intraparenchymatous cyst, (2) subcapsular cyst, (3) pararenal cyst and (4) parapelvic cyst (situated in the hilus). The majority of cysts treated surgically have belonged in group 2; that is, they have reached the external surface of the kidney at a certain time in their development, after starting within the renal parenchyma.

The etiology and pathogenesis are not yet known, but such a cyst is probably of embryologic origin. It is surprising to note that all authors apparently agree in identifying the pathologic anatomy of the solitary cyst with that of cystic kidney, holding that the same factor produces now a large cyst and now a cystic kidney and that there is only a quantitative difference. Lindenfeld does not agree with this idea. Solitary cyst is only a benign condition in an excellent degree, its very

16. Lindenfeld, L.: *Kystes solitaires du rein. Étude clinique et expérimentale*, J. d'urolog. 38:506-517 (Dec.) 1934; 39:18-35 (Jan.); 119-130 (Feb.) 1935.



existence often being discovered only by accident. It endangers neither life nor the kidney, which for the most part remains functionally unimpaired. Cystic degeneration of the kidney as a rule (in 80 per cent of cases) is a bilateral condition and often is hereditary. In the adult it appears in a form comparable to nephrosclerosis and may even cause death by uremia. The two conditions, cysts and cystic degeneration, are entirely unrelated. The solitary cyst of the kidney consists of a kidney with a cyst; the cystic kidney is a large kidney honeycombed with small cavities, like a sponge. In the former, the parenchyma is sound; in the latter, destruction has begun and terminates fatally. In the solitary cyst, the epithelial lining is often wanting; in the cystic kidney it is present and in a state typical of degeneration.

Lindenfeld's explanation of the embryologic origin of the solitary cyst of the kidney is, briefly, that the kidney develops from two buds, both from the mesoderm: the secretory portion from the blastema of the kidney and the excretory portion from that of the ureter, which latter is also the germ of the primitive renal pelvis. The excretory ducts undergo a frequent division and push, as they grow, into the tissue of the blastema of the kidney, which they surround. This tissue is, so to speak, torn by the process and becomes subject to detachment and displacement, thus giving origin in rare cases to what will become a cyst in its later development. The cyst thus formed grows toward the surface of the kidney, and then, becoming free from the pressure of the surrounding parenchyma, finds conditions more favorable for its continuous development.

On the basis of this view, Lindenfeld performed experiments on animals to produce artificially the analog of a congenital cyst. After removing one kidney, he took pieces of its mucosa and transplanted them to the remaining kidney, at the same time, for purposes of comparison, grafting into the kidney pieces of another mucosa, that of the gallbladder, for which reason he also performed cholecystectomy on the animals; in some of them he also applied pieces of striped muscle as a control. The animals were kept under observation for from five to one hundred and eighty days. The results revealed that cysts developed in 70 per cent of the animals which had received subcapsular transplants of mucosa from the urinary tract; mucosa from the gallbladder also produced cysts, but of a different character. It appears, therefore, that the view that a solitary cyst of the kidney may arise from the detachment or the unlacing of a part of the germs of the excretory system of the urinary tract is well founded.

The only proper treatment of these cysts is surgical. Puncture is not satisfactory, since in 50 per cent of such cases the termination is fatal. The old method of incision left fistulas and is justifiable only

if there is suppuration of the content of the cyst. The ideal treatment is enucleation of the cyst. This was easily accomplished in 3 of Lindenfeld's 5 cases. But sometimes there are such dense adhesions to the renal parenchyma that the latter is injured in the process; in such a case it is necessary only to suture the small wound thus made to obtain perfect hemostasis. If the cyst extends to the bottom of the parenchyma, partial nephrectomy may also be unavoidable, but the results have not been satisfactory, as fistulas remain. In view, also, of the dangers of hemorrhage from such resection, it may be necessary to remove the entire kidney under such conditions to stop the bleeding. But this should be done only in the rarest cases. If the kidney must in some cases be partly removed, resection *en collerette*, as performed by Albarran, Marion and others, would seem the best method. The best approach is by a lumbar incision. At the end of the procedure, nephropexy should be effected to prevent ptosis of the kidney into the cavity previously formed by the cyst. In conclusion, the most important point is stressed: that the kidney should be conserved whenever possible, when the cyst is removed, since the organ is, as a rule, healthy in these cases.

*Hydronephrosis*.—Blanc and Guérin<sup>17</sup> described an unusual case of bilateral hydronephrosis in which a pregnant woman was suffering from two different types of this condition, the one congenital and the other acquired as the result of a congenital predisposition through abnormal vascularization of the kidney. On the left side the hydronephrosis, unaccompanied by ptosis, involved only the pelvis and calices, which it had completely destroyed; it began at the level of the vascular band, without involving the ureter, thus showing that it was not of the primary congenital type; there was no doubt of the rôle played here by the anomalous vessel in its formation. According to the authors, there can be no congenital hydronephrosis that is not also a hydro-ureteronephrosis, that is, a dilatation of the entire excretory tree, a condition that was, on the other hand, present on the opposite (right) side in the case under consideration. The left kidney was removed when the patient was two months pregnant; six weeks later the right kidney, which was eliminating only 31 per cent of phenolsulfonphthalein both before and after nephrectomy on the left side, and which was therefore not compensating, was found on intravenous pyelography to be both ptosed and hydronephrotic with a ureter that was dilated and sharply kinked a little below the ureteropelvic junction. With a conviction that the prognosis was too grave if this solitary kidney with inadequate

17. Blanc, Henry, and Guérin, Pierre: Considérations sur un cas d'hydronephrose bi-latérale chez une femme enceinte opérée de néphrectomie gauche et de néphropexie droite, *J. d'uro.* 39:208-218 (March) 1935.

function were left in its abnormal position to be subjected to the inevitable compression that would result in the later months of pregnancy, besides the danger of infection from urinary stagnation, nephropexy was carried out on the right side when the patient was four months pregnant. It was the authors' view that this operation should be followed immediately by a therapeutic abortion, but from religious considerations this was not permitted by certain colleagues, and the pregnancy, not without serious misgiving, was allowed to go on to what proved after all to be a successful termination, although it was followed by a renovesical colon bacillus infection.

It is altogether probable in this case that if a diagnosis of congenital hydronephrosis of the right kidney had not been made at the time of nephrectomy on the left side and if there had been occasion to take a pyelogram in the sixth or seventh month of pregnancy, the case would have been regarded as a perfect example of uretero-hydronephrosis of pregnancy. The authors expressed the belief that a considerable number of cases in which the condition has been termed hydronephrosis of pregnancy were in fact instances of congenital hydro-nephrosis, merely revealed at the time of pregnancy.

The remarkably good results in this case, in which the hydro-nephrosis receded to a certain extent during the year after accouchement and in which the functional capacity of the remaining kidney greatly improved must certainly be attributed to the nephropexy. The case clearly proves that pregnancy does not constitute a contraindication to operation. On the contrary, by freeing and straightening the ureter, thereby improving the conditions for evacuation of the urine, it was possible to prevent probable grave infection, since lavage of the renal pelvis could be carried out throughout the remainder of the pregnancy.

Notwithstanding these excellent results, the authors stated that if a similar condition should arise in their practice they would prefer not to take the risk that was here involved, but would unhesitatingly advise the interruption of the pregnancy at an early period.

*Renal Glycosuria.*—Wade<sup>18</sup> emphasized the difference between renal glycosuria and glycosuria that is the result of diabetes mellitus. He stated that renal glycosuria is a not uncommon cause of the presence of sugar in the urine. The criteria essential to the diagnosis of this condition are: (1) the presence of dextrose in the urine without other sugars or reducing substances, (2) the raising of the curve for blood sugar after the oral administration of dextrose from a normal fasting level of from 80 to 120 mg. per hundred cubic centimeters to 180 mg. or more half an hour later. This value for blood sugar then drops to

18. Wade, J. L.: A Consideration of Renal Glycosuria, *Proc. Staff Meet., Mayo Clin.* 11:346-349 (May 27) 1936.

a lower level at the end of the second hour, and at the end of the third hour it is down to, or below, the normal fasting level. Sugar must appear in the urine in at least one specimen taken during the test. Glycosuria must accompany a normal level of blood sugar. Renal glycosuria may be continuous, or it may be intermittent or cyclic.

The diagnosis of renal glycosuria has been made in 146 cases. Males predominated in the series in the ratio of 3:1. Many of the patients had thought, or had been told, that they had diabetes mellitus and had taken insulin for some years prior to the time the correct diagnosis was made. In many instances the presence of renal glycosuria is undoubtedly never discovered as the condition is frequently symptomless. Questionnaires were sent to the patients in an effort to determine their state of health. Eighty-eight replies were received. In not 1 of the 88 cases did diabetes mellitus develop. This observation is in accord with other articles on this subject.

*Lymphatics.*—Jasienski<sup>19</sup> undertook to study more precisely than has hitherto been done the anatomic details of the lymphatics of the renal parenchyma, using young dogs for his experiments, since the lymphatics reveal the closest resemblance to those of man. Unlike other experimenters in this field, he injected the color dye in situ into the kidneys of living dogs, without even displacing the organs, so that the circulation continued to be normal; not until the entire amount of the dye had been introduced slowly and without the least pressure did he proceed to remove the kidney. In this way he succeeded in filling the lymphatics with coloring substance under conditions that were approximately physiologic.

The arrangement of the lymphatics in the parenchyma is so characteristic that it is impossible to confuse it with that of the blood capillaries, when a proper technic is used, but this presupposes not only the cutting of very thin sections but their immersion in water during examination, without which the finest of the lymphatics do not become visible. It was necessary to examine over 20,000 sections before clear results could be obtained, for until one is well experienced with the technic one may frequently inject the color dye into venules as well as lymphatics, a circumstance which has led to much confusion among the various authors.

In order to know the lymphatic system in its ensemble, it is necessary to note separately the character of the lymphatics of the capsule and those of each one of the elements composing the parenchyma. The capillary network of the capsule is composed of relatively large nodes, but the size is subject to considerable variation in the different sectors.

19. Jasienski, George: Les lymphatiques du rein sain, J. d'urol. 40:97-123 (Aug.) 1935.

Examined under oil immersion, the numerous sinuous enlargements of the canals present the appearance of cylindric spaces which alternately enlarge and contract, and from which start short ramifications with clearly defined contours and irregular form. The abundant intracap-sular network, the plexuses of which extend almost parallel to the surface of the kidney, communicates directly with the network of the parenchyma, its numerous canals anastomosing as they pass toward the latter. The size of the meshes is subject to wide variations. Within the cortical substance every tubule, every glomerulus and every part of the blood vessels is surrounded with a rich lymphatic reticulum; the lymphatics even penetrate within the glomerulus as it accompanies the afferent vessel.

Outside of the hilus the collecting lymphatics of large caliber unite to form the trunks of the pedicle of the kidney, which are provided with valves; in addition, the network of the medullary substance communicates with that of the calices, pelvis and ureter.

Even under oil immersion the smallest lymphatic capillaries of the renal parenchyma are so extremely fine that their walls cannot be distinguished, but the uniformity of their contours and their characteristic undulatory appearance justified the conclusion that they are provided with these. A study of the large ones reveals a wide variety of form and shape, some being separated by large triangular spaces and others by rounded, oval or stellate spaces or spaces forming less geometric patterns. All these spaces intercommunicate by ramifications which create the multiform meshes of the network. They give off undulating branches, which are much finer than the blood capillaries and which cross the intertubular spaces and the tubules in all directions, without following them as do the arterial and venous capillaries. These characteristics, accordingly, distinguished the two vascular systems from each other. The blood vessels, too, the walls of which can be clearly distinguished here and there, are surrounded by a close-meshed lymphatic reticulum in a design that repeats itself regularly, and of which the most characteristic feature is the great number of enlarged spaces, which are provided with prolongations that sometimes make them resemble nerve cells. The character of the network depends on the caliber of the blood vessel it surrounds.

Injection into the lymphatic reticulum of the medullary substance of the kidney is attended by such great technical difficulties that it is successful only in exceptional cases. Jasienski succeeded a few times, by accident, in making intraparenchymatous injections in the superficial layers of the cortex which by chance carried the substance injected into small portions of the parenchyma. He was able, therefore, to see that

the surface of some of the straight tubules is covered with a rich network of lymphatics recalling those of the cortical substance, but it is much less fine and the anastomoses are less frequent than in the cortex, so that the meshes appear larger and seem to be prolonged in a vertical direction. Contrary to what is observed in other tissues and organs, the lymphatics of the renal parenchyma preserve neither their individuality nor their caliber for any great distance but are distinguished by a much richer arborization than that of the blood vessels. Everywhere there is a mixed network, with no large collecting trunk continuing over a single course, until the hilus is reached, when such trunks appear on the renal pedicle. All the pericapillary lymphatics pour their content into the perivascular networks. The respective networks of the capsule, cortex and medulla are not independent of one another: They constitute a single continuous system, composed of the ensemble of the small reticula which are in contact with all the histologic elements of the parenchyma.

*Perirenal Lipomatosis.*—Lieberthal,<sup>20</sup> in a routine examination of several thousand kidneys from surgical and postmortem material, found definite and significant changes in the perirenal and peripelvic fat in more than a hundred kidneys. From these he reconstructed chronologically the changes of perirenal and peripelvic fibrolipomatosis from the onset to the end-stage, the so-called replacement lipomatosis of the kidney. This is supposed to be a rare condition, but it is merely an advanced form of the peripelvic lipomatosis which accompanies every chronic suppurative process in the kidney. The changes in the peripelvic fat are secondary to the chronic inflammatory process present in the kidney, usually chronic or recurring pyelonephritis with atrophy and substitution of connective tissue.

Some authors assume that changes in the kidney are those of pressure from active proliferation and overgrowth of the peripelvic fat, but this is erroneous. Lieberthal gives illustrations of these changes, from early lipomatous hyperplasia (a hyperplasia ex vacuo) in the renal contracture of benign nephrosclerosis, chronic glomerulonephritis and chronic pyelonephritis to complete replacement lipomatosis, as seen in pyonephrosis caused by calculus.

The clinical significance of the changes lies in the altered renal topography, which makes operation on the kidney difficult at times. A detailed knowledge of these changes is essential to safe and expeditious operation.

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20. Lieberthal, Frederick: *Perirenal and Peripelvic Fibrolipomatosis: Their Relation to Replacement Lipomatosis of the Kidney*, Surg., Gynec. & Obst. **61**: 794-801 (Dec.) 1935.

*Nephro-Ureterectomy.*—Papin and his associate,<sup>21</sup> after a glance at the history and a study of the anatomy of the region, reviewed the various technics for nephro-ureterectomy and described the routes of approach and the various incisions that have been used for accomplishing this combined procedure, together with the indications for each.

Among conditions that call for nephro-ureterectomy are the presence of calculi, when they have caused grave injury to both kidney and ureter, hydronephrosis and pyonephrosis, pyo-ureter, ureters with vesical reflux, cases of anomalies of the ureter and finally tumors involving the pelvis and ureter in which the entire reno-ureteral apparatus must be removed en bloc. With some reservation, renal tuberculosis may be regarded as suitable for this operation, but formal indications for this have been rare.

The long lumbo-iliac incision of Albarran and of Israel, used by most surgeons when a large kidney with large ureter has to be removed, runs from the twelfth rib (from the angle formed by it and the sacrolumbar mass) to the level of the anterosuperior iliac spine, at a point 2 fingerbreadths within it. Its disadvantages are the fact that the integrity of the abdominal and lumbar wall is injured, making suture of muscles in at least two planes necessary, and that many nerve filaments are cut, especially those from the tenth, eleventh and twelfth intercostal nerves; since these are motor filaments to the great oblique muscle, an incision too far forward may section filaments of the large and small abdominogenital nerves, it being impossible not to cut some of these branches. In addition, the two sides of the abdomen are left unequal, with the side operated on bulging. Although there may be no true eventration, there must always be weakness of the wall.

More satisfactory is the combined incision, that is, two incisions, one high and one low, leaving between them a strong segment of wall, as wide as possible. The upper incision is always a lumbar incision; it is sometimes the one first made, but often it follows the low incision. It should be made as short as possible, consistent with the size of the kidney. In order not to lose operating space at the upper end, the lumbo-costal ligament must be cut close to the twelfth rib. When the lower incision, to free the ureter, has been closed, the patient is placed in the nephrectomy position. Then, after the lumbar incision has been made, it is possible to ligate and section the vascular pedicle at once and to extirpate the ureter from below upward; the ureter may first be extirpated and the renal pedicle tied afterward.

If the lumbar incision has been made first, without knowing in advance that a ureterectomy would be required, as, for example, when

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21. Papin, E., and de Berne-Lagarde, Jean: Indications et technique de la néphro-urétérectomie totale et subtotale, *Arch. d. mal. d. reins* 10:1-62 (Jan.) 1936.

a supposed tumor of the kidney turns out to be a tumor of the pelvis, one of the two following procedures may be carried out: 1. The kidney is removed, and the ureter is sectioned as low as possible between two ligatures; the lower stump is enveloped by a compress and solidly tied up with a silk or linen thread, and the wall is closed completely. 2. As soon as the necessity of removing the ureter is discovered, the lumbar wall may be closed only temporarily, with one or two skin sutures, a temporary dressing applied and the patient placed on his back while the pelvic incision is made for section of the ureter. The lower ureteral stump is prepared in just the same way, but through the pelvic incision, the ureter being separated as high up as possible; the pelvic incision is then closed, and the surgeon returns to the lumbar incision, to complete the operation by the usual technic. The latter procedure is long and tedious but has the advantage, in case of malignancy, of avoiding the section of a neoplastic organ.

Again, the lower part of the ureter may be reached by the hypogastric incision, which may take any of several forms, lateral, median, paramedian or mixed. The best known among these are the lateral incisions of Albarran, of Gibson and of Beer, the oblique incision of Gutierrez, the inguinal incision of Mazzoni and the various incisions devised by Herrick, Kidd, MacBurney, Pfannenstiël, Judd, Scholl and others. The incision most commonly used is that in the median vertical suprapubic line, from 12 to 15 cm. long, known in the United States as the incision of Judd. Whatever the technic for reaching the bladder by the median subperitoneal route, any of several procedures may be employed to expose the ureter, namely, (1) lateral décollement of the bladder, (2) total décollement of the bladder, (3) extraperitonealization of the bladder and (4) cystotomy, all of which are described.

For subtotal nephro-ureterectomy, the lumbar incision is always sufficient and can be prolonged downward according to need. The ureter is sectioned under full vision and as far down as possible between two ligatures or two clamps; Papin and his co-worker prefer the clamps. For a juxtavesical nephro-ureterectomy, the very long lumbar incision may be used, the only part of the technic that varies being at the lower segment of the ureter. 1. The entire ureter may be removed, and the vas deferens or the uterine pedicle sectioned, or if no adhesions are present, the ureter may be slipped upward from below, under these structures without cutting them. 2. The ureter may be removed in two segments, cutting it above the vas deferens or uterine pedicle and removing the lower segment separately, as may be necessary in case of calculus.

The authors concluded that the median route for exposure of the ureter has the most advantages, as follows: 1. In many cases the peritoneum need not be opened. 2. If necessary, the extraperitonealization



of the bladder gives an excellent exposure of the terminal part of the ureter. 3. If the bladder for any reason needs to be opened, there could be no more convenient route. 4. No other incision can compare with this one in its preservation of the solidity of the wall and the certainty of not injuring nerve filaments.

#### ADRENAL GLANDS

*Adrenogenital Syndrome.*—Broster<sup>22</sup> defined the adrenogenital syndrome as a condition in which secondary male sex characteristics appear in the female associated with retrogression of the primary and secondary female sex characteristics and their functions. The clinical picture is determined by the type of lesion and the age of the patient and is composed of the following abnormalities: the appearance of hair in females in masculine distribution; alterations in bodily contour resembling that of the male; immature development of the genitalia, both external and internal, and psychologic abnormalities.

The following classification of cases was made:

Group 1. Adrenal pseudohermaphroditism. This is the most complete form of the syndrome, in which changes occur before the bodily form and sex organs have become differentiated. There are marked virilism and hypertrichosis of the male type, primary amenorrhea, and normal feminine development has not taken place.

Group 2. Adrenal virilism. This later variety, in which the adrenal changes set in after puberty, is associated with alterations in bodily form, and in the external sex organs, hypertrichosis of the male type, and disturbance of sex functions. A relatively large number of patients belong in this group.

Group 3. The Achard-Thiers syndrome. The adrenal lesion appears to be one element in a multiglandular syndrome. These patients presented the symptom complex described by Achard and Thiers as "diabetes of bearded women." The chief symptoms are the male type of hypertrichosis of the face, obesity, glycosuria with decreased carbohydrate tolerance, hypertension, and usually amenorrhea, but without other signs of virilism.

From observations of 60 cases in which virilism in varying degrees was present, the author concluded that laboratory investigations usually give negative results and that the only method by which to detect adrenal hyperplasia is exploratory laparotomy. A subdiaphragmatic approach similar to that used for the kidney is employed. Patients subjected to unilateral adrenalectomy have evidenced no ill effects so far as their general physical condition is concerned, and there has been a definite tendency toward loss of hair and restoration of menstrual function. The largest adrenal gland removed measured 7.5 by 7.5 cm.; one of the smallest measured 4 by 2.1 by 1.5 cm. The author concluded

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22. Broster, L. R.: Eight Years' Experience on the Adrenal Gland, Proc. Staff Meet., Mayo Clin. 11:200-202 (March 25) 1936.

that virilism is not necessarily dependent on hypertrophy alone, as it may be associated with apparently normal adrenal glands.

Unilateral adrenalectomy was performed in 23 cases without a fatality. A specific differential staining quality in the cells of the adrenal cortex was found, which is evident in the reaction to the Ponceau-fuchsin stain. This quality is absent in controls but is present in the tumor cells in cases of virilism due to neoplasm. It was also present in the fetus of both sexes, and virilism can be explained by its abnormal persistence in the female. This abnormality, the author suggested, may account for the clinical syndrome evidenced by the patients in groups 1 and 2. He expressed the belief that in cases in group 3 the normal restrictive action of the pituitary body on the masculinating potentialities of the adrenal gland in the female may fail to be maintained. This type of case would then be associated with pituitary dysfunction, and the clinical picture would vary, depending on the predominance of one or the other factor.

*Tumor.*—Cahill, Loeb, Kurzrok, Stout and Smith<sup>23</sup> stated that tumors of the cortex of the adrenal gland may occur without virilism. The following endocrine changes may accompany their occurrence: pseudohermaphroditism (female); premature puberty in the male; growth maturity with masculinity in female children; hirsutism, amenorrhea and adiposity in adult females; an indistinct picture with adiposity after the menopause, and possible inversion changes in male adults.

Removal of a tumor of the adrenal gland by the transperitoneal route is the most satisfactory surgical procedure. In a certain percentage of cases collapse follows the removal of this gland. Removal of the tumor produces a symptomatic cure of the endocrine symptoms but has no effect on the anatomic changes in the pseudohermaphrodite. Metastasis of these tumors produces the same endocrine changes as the original growth. The tumor that produces the endocrine changes has cells which greatly resemble the reticulate layer of the adrenal gland and have an increase in fuchsinophilic granules over normal. The adrenal cortex hormone has not been demonstrated in these growths.

#### BLADDER

*Tumor.*—The Committee of Carcinoma Registry<sup>24</sup> reported 1,354 tumors in the registry in 1936; in 658 cases operation was performed

23. Cahill, G. F.; Loeb, R. F.; Kurzrok, R.; Stout, A. P., and Smith, F. M.: Adrenal Cortical Tumors, Surg., Gynec. & Obst. **62**:287-312 (Feb. 15) 1936.

24. Committee of Carcinoma Registry: Cancer of the Bladder; a Study of the Five-Year End Results in 658 Epithelial Tumors of the Bladder in the Carcinoma Registry of the American Urological Association, J. Urol. **35**:481-490 (April) 1936.

more than five years before. The record as to the final disposition of these 658 cases is complete, with the exception of 18 cases. Of the 658 patients operated on more than five years before, 151 were alive at the end of five years, a simple crude survival rate of 23 per cent. Of these 151 survivors, 104, or 15.9 per cent, were without evidence of disease by sign, symptom and cystoscopic examination. The remaining 47 survivors revealed some evidence of recurrence or metastasis.

There is nothing remarkable about the age or the sex incidence, but it has been found that among patients under the age of 50 years the tumor in both sexes was of high grade of malignancy in 50 per cent of the cases, whereas among the patients after the age of 50, carcinoma of low grade preponderated. There seems to be no relation between sex and grade.

Of the 151 patients who survived for five years, 37, or 24.5 per cent, had a tumor of grade 3 or 4, while 111, or 75.5 per cent, had a tumor of grade 1 or 2. The degree of malignancy of the tumor influences the end-result. Of 133 patients with a tumor of grade 1, 61, or 45.9 per cent, survived five years. Of 194 patients with a tumor of grade 2, 50, or 25.7 per cent, were alive at the end of five years. Of 244 with a tumor of grade 3, only 34, or 13.9 per cent, survived five years. Of 70 cases in which the tumor was of grade 4, in only 3, or 4.3 per cent, was the lesion under control at the end of the five year period. In the entire series of 658 cases, 312 tumors were known to be papillary, whereas 245 were classified as infiltrating. In the remaining 41 cases the lesion was not so classified. Of the 151 patients who survived for five years, 109 had a tumor classified as papillary and 34 as infiltrating, and the type of 8 of the tumors was unknown. Thus, of the 143 tumors that were classified, 34 infiltrating tumors, or 24.9 per cent, were controlled. The influence of neoplastic infiltration is further demonstrated by the result obtained in the papillary group and in the infiltrating group in the entire series. Of 312 patients with a papillary tumor on whom operation was performed more than five years ago, 109, or 34.9 per cent, survived five years, whereas of 245 with an infiltrating tumor 34, or 13.9 per cent, were cured. The size of the tumor when first seen is also related to the result at the end of five years. One hundred and twelve tumors were stated to be less than 2 cm. in diameter when first seen. Three hundred and nine varied from 2 to 5 cm. in diameter, while 222 were larger than 5 cm. in diameter. The size of 15 tumors was not stated. It is an interesting commentary on the usual delay in the diagnosis and treatment of tumor of the bladder that only 112 of the 658 patients, or 18.5 per cent, came under observation when the tumor was still less than 2 cm. in diameter. Yet it is in this very group that the largest percentage of five year cures was obtained, namely, 34 of

112 cases, or 30.3 per cent. When the tumor varied from 2 to 5 cm. in diameter, 82 of 309 patients, or 26.5 per cent, survived five years. However, when the tumor was larger than 5 cm., in only 35 of 222 cases, or 15.8 per cent, was the growth under control for five years.

The open surgical method, combined in the majority of cases with the use of physical agents, was the treatment of choice in 468 of the 658 patients. One hundred and forty-five patients were treated by closed methods without surgical intervention.

Of 468 patients operated on, 29 patients died after operation, an operative mortality for the series of only 6.2 per cent. Of 27 on whom partial resection of the bladder was performed, 7 died after operation, a mortality of 26 per cent. Cystotomy with excision of the tumor and without the use of physical agents was used on 105 patients, 5 of whom died after operation, a mortality of 4.9 per cent. Cystotomy with the implantation of gold radon seeds was used in 147 cases, after which 3 patients died, a mortality of only 2.05 per cent. Cystotomy with fulguration as the principal form of physical therapy was utilized in 121 cases, followed by 9 postoperative deaths, an operative mortality of 7.4 per cent. In 66 cases the bladder was opened, and the actual cautery was applied to the tumor, following which 4 patients died, a mortality of 6.1 per cent. The mortality in the closed methods of treatment was as follows: Of 54 patients treated by the cystoscopic implantation of gold seeds of radon, 2 patients died; or 3.9 per cent. After cystoscopic fulguration of 76 patients, 5 patients died, or 6.6 per cent.

In 27 cases in which partial resection of the bladder was done for tumor, 8 patients, or 29.6 per cent, survived five years. Of the 8 survivors, 3 were alive at the end of five years with recurrence or metastasis. Hence, only 5 patients, or 18.5 per cent, of the 27 so treated were entirely without evidence of disease by symptom and cystoscopic examination at the end of five years. One hundred and five patients were treated by cystotomy and simple excision of the tumor. Of these, 34, or 32.4 per cent, survived five years. Cystotomy with the implantation of gold seeds of radon was utilized in 147 cases, and 24 patients, or 16.3 per cent, were living at the end of five years. Only 13 patients so treated, however, were without evidence of disease at the end of five years (8.8 per cent). Cystotomy with fulguration was the method of choice in 121 cases. Of these, 30 patients, or 24.8 per cent, lived five years. Eighteen of the patients, or 14.8 per cent, were without cystoscopic evidence of disease at the end of that time. Of 66 patients treated by cystotomy and the application of actual cautery, 12, or 18.2 per cent, were alive at the end of five years, and 8, or 12.1 per cent, of these revealed no evidence of recurrence or metastasis.

Of 54 patients treated by the cystoscopic application of radium, 11, or 20.4 per cent, were alive at the end of five years. Of these 11, 8, or

14.9 per cent of all patients so treated, revealed no cystoscopic evidence of disease at the end of five years. Seventy-six patients were treated exclusively by cystoscopic fulguration. Of these, 29, or 38.2 per cent, survived five years. Twenty-five, or 32.9 per cent of the whole, were without cystoscopic evidence of disease at the end of five years. Fifteen patients in whom the condition was hopeless were treated by means of roentgen rays, and 2 survived five years, 1 without evidence of disease at the end of that time.

Quinby<sup>25</sup> stated that at the Peter Bent Brigham Hospital patients on whom total cystectomy has been performed have been chosen on the following criteria: The growth must be on the lower segment of the bladder so that its removal would involve the sphincter or orifice of the ureter or both; there must be no demonstrable metastasis to the regional lymph nodes or to those of the aortic area; on one side at least the excretion from the kidney, its pelvis and ureter must be normal, and, finally, microscopic examination must reveal evidences of actively growing carcinoma.

At the time of this report, 10 patients had been treated by total cystectomy and uretero-intestinal anastomosis. One patient, a woman, was alive more than three years after operation. There was no evidence of recurrence. Of the other 9 patients, 2 died as a direct result of operation which was imperfect in some way. The remaining 7 patients died of recurrent carcinoma at shorter or longer periods after operation. In none of these, however, was there any further acute difficulty in the urinary tract. The patient who survived the operation the longest lived for eight years after cystectomy. Until the last year of his life this patient had been well and active. Signs of recurrence of the malignant lesion then appeared in the region of the lower part of the rectum, and the man died about twelve months later.

From Quinby's experience with these patients, especially when comparing their postoperative careers with those of patients in whom carcinoma of the bladder has been treated by radium or various combinations of radium and partial excision, he concluded that total cystectomy should be employed more often than has been done in the past in the treatment of carcinoma of the bladder.

Keyes, Ferguson and Hocker<sup>26</sup> stated that a single tumor of the bladder which is of grade 1 or grade 2 malignancy may be satisfactorily treated by such methods as fulguration, implantation of radon seeds and resection. If the tumor recurs, it is classed as multiple. Multiple

25. Quinby, W. C.: Indications for and Results of Total Cystectomy for Cancer of the Bladder, *New England J. Med.* **212**:501-503 (March 21) 1935.

26. Keyes, E. L.; Ferguson, R. S., and Hocker, A. F.: Roentgenotherapy for Recurring Bladder Tumors of Low Malignancy: A Preliminary Report, *Tr. Am. A. Genito-Urin. Surgeons* **28**:265-269, 1935.

tumors recur after any treatment. It has been estimated that recurrence occurs in half the cases in which the tumors are multiple. Recently a form of roentgen therapy that does not cause roentgen sickness or grave irritation of the skin has been employed. Vesical rather than cutaneous sensitivity limits this treatment. Tumors of a low grade of malignancy and of slight cellular differentiation are especially vulnerable to this form of treatment.

Until recently, roentgen therapy has been applied to the full erythema dose. The usual dosage is as follows: 200 kilovolts, from 4 to 25 milliamperes, a filter of 0.5 mm. of copper and 1 mm. of aluminum and a skin-target distance of 50 cm. From two to four treatments are given at intervals of from four to seven days. Skin tolerance limits the treatment. Coutard has shown that excellent results may be expected if each dose of roentgen rays is reduced from 700 roentgens to 300 or 400 roentgens, exposure to the rays being repeated daily for eighteen or twenty days. By Coutard's therapy the effect on the surface is less, and the deep effect is greater. Thus roentgen ray sickness is less, but irritation of the bladder and of the bowel is considerable.

Ferguson determined on the following set-up: 200 kilovolts, 25 milliamperes, a filter of 1.7 mm. of copper and 1 mm. of aluminum and a skin-target distance of 100 cm. Four portals are employed, one over each rectus muscle and one over each buttock; these are to be irradiated in pairs each alternate day. The duration of irradiation is fifteen and a half minutes, whereby a dose of 100 roentgens is delivered to each portal. The total dose is 3,000 roentgens to each portal, more or less. By this method an increase of from 15 to 20 per cent in dose of effective radiation at a depth of 10 cm. is obtained. The treatment is continued for from forty-five to sixty days. The results with this method of treatment have been absence of roentgen ray sickness, relief of spasms of the bladder as far as they are due to tumor, checking of hematuria in the second or third week and minimization of cutaneous irritation. The irritation of the bladder is mild. If the patient is urinating about every hour, this irritation does not increase. This therapy has been applied to tumors in various parts of the body with comparable results. If cystoscopy is performed within a month after treatment, the mucosa will sometimes appear inflamed and sometimes normal. An effort has been made at intervals of two weeks during treatment to destroy the tumor. One day the tumor will be there, revealing some cellular disintegration, and the next day it will be gone.

Thirty tumors of the bladder were treated by irradiation in divided doses. Various modifications of Coutard's technic were employed until January 1935. Since then the author's own technic as described has been used in 12 cases. There was 1 relapse and no deaths; in 4 cases subsequent cystoscopy revealed no tumor, and 8 patients are doing well

but are still under treatment. Four of 30 patients had died, 1 was not relieved, 1 had a recurrence and 16 have been relieved from their symptoms and cystoscopy did not reveal a tumor.

Parmenter and Leutenegger<sup>27</sup> stated that hematuria, with or without vesical disturbance, is the cardinal symptom of tumor of the bladder. In their series it was present in more than 90 per cent of the cases. Fulguration seems to be curative in cases of benign papilloma. It is simple to apply and rapid in its effect and has slight morbidity and no mortality. Its use should be limited to benign papillomas, regardless of the fact that it is sometimes apparently curative in malignant conditions. In the cases in which the papilloma was malignant there were about the same number of five year cures when fulguration alone was used as in those in which fulguration and radium were used. The number of patients in the fulguration-radium division was numerically less by about 33 per cent. It was also noted that the length of life was longer in a greater number of these, that the effect on the tumor was more pronounced, that the recurrences were fewer and that the time interval between was greater. Fulguration alone, with its necessity for constant repetition, is conducive to infection, promotes and augments its severity, probably agitates and excites the tumor too much and carries a high mortality, particularly fulguration by the suprapubic method of approach. In at least 6 or 7 patients, the dose of radium seemed inadequate; when a large dose was used a somewhat better result was noted. Resection unless thoroughly performed does not offer an aid to treatment. The death rate is high, and the end-results are poor. A study of the cases of carcinoma disclosed the futility of fulguration alone. The group in which radium was used revealed a more noticeable effect on the tumor, longer periods of freedom from recurrence, greater span of life and practically no mortality. The patients who received the large doses of radium seemed to obtain the most satisfactory results.

*Stones.*—Higgins,<sup>28</sup> in his experiments, found that when animals were given a diet deficient in vitamin A for two hundred and fifty days necropsy revealed the presence of vesical calculi in 88 per cent and of renal calculi in 42 per cent. It likewise was shown that if vitamin A alone was added to the diet the formation of calculi was prevented. It has been stated that calculi have been produced experimentally only in white rats, a species remote phylogenetically from man. Therefore, a group of 7 dogs was maintained on a diet deficient in vitamin A for

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27. Parmenter, F. J., and Leutenegger, C. J.: Bladder Tumors, *J. Urol.* **35**: 316-320 (March) 1936.

28. Higgins, C. C.: Further Observations on the Experimental Production of Urinary Calculi, *Tr. Am. A. Genito-Urin. Surgeons* **28**:157-162, 1935.

eleven months. Cystotomy was performed on 4 of these animals, under ether anesthesia. Multiple stones were found in the bladders of 3, and neither stone nor sand was noted in the fourth dog.

The possibility of producing calculi composed of uric acid and urates was then considered. The fact that birds eliminate uric acid and that the majority of the urea is converted into uric acid was well known. Therefore, observations were made on a group of chickens placed on a diet deficient in vitamin A. At necropsy, five months later, the kidneys were found to be somewhat pale and to contain urates and sand, and the ureters contained urates and small calculi of uric acid. Hard concretions of uric acid were present in the cloaca. In order to produce calculi similar to stones in the bladder, colostomy was performed on the chickens, thus diverting the fecal stream and utilizing the lower segment of the bowel and the cloaca as a bladder. From this structure, small calculi were easily removed for chemical examination, which revealed that they were composed purely of uric acid and urates.

*Obstruction of the Neck of the Bladder.*—Caulk<sup>29</sup> stated that the development and perfection of instruments of small caliber, the tolerance of infants and children to instrumentation when judiciously performed and the cooperation of the pediatrician in seeking special investigation of the urinary organs of children have tended to advance the urologic treatment of infants and young persons. Obstructions along the urinary tract are common and occur mainly at the normal physiologic constrictions, the ureteropelvic juncture, the intravesical ureter and the internal orifice of the bladder.

The clinical pictures resulting from obstructions in different portions of the urinary system may be similar, and the general physical signs may appear misleading. For practical purposes, and as an aid to the clinician, there are certain diagnostic procedures which may be helpful. The first is the determination of the total renal function by tests of elimination with drugs such as phenolsulfonphthalein or by tests of retention secured through a determination of the blood for its nitrogenous elements. The presence or absence of residual urine should be determined. If it is present, it usually indicates that the condition results from obstruction at the internal orifice of the bladder and is probably bilateral. The cystogram may afford information in revealing the topographic outline of the urinary system. Intravenous urography may be serviceable for delineating the outline of the urinary tract, but in Caulk's experience this method has not been entirely reliable. Cystoscopy is usually necessary before any definite plan of corrective therapy may be satisfactorily applied, and children tolerate this type of manipulation

29. Caulk, J. R.: Obstructions at the Bladder Neck in Infants and Children, Tr. Am. A. Genito-Urin. Surgeons 28:287-296, 1935.



satisfactorily. Anesthesia was required in only 35 per cent of the cases. The importance of regurgitation of the contents of the bladder into the ureters and renal pelves cannot be overestimated.

Fourteen punch operations and 2 suprapubic operations were performed on 16 children because of obstruction at the neck of the bladder. Six operations were performed because of valves, 1 because of valve and bar, 7 because of contracture of the neck of the bladder and 2 because of lobules. The child's punch was used in 9 cases and the baby punch in 5. All of the children who had residual urine and gave evidence of urosepsis received preliminary treatment by drainage with an indwelling catheter, copious flushing of the bladder and urinary antiseptics, frequently by subcutaneous injections of saline solution and intravenous injection of solutions of dextrose and occasionally by transfusions, until their condition appeared sufficiently satisfactory for any type of operation.

The punch with its obturator was passed into the bladder, which had previously been filled with sterile water or a solution of boric acid. For infants the baby punch, no. 14 French, was used, and for larger children the child's punch, no. 18, was employed. After the introduction of the instrument, the obturator was removed, and the instrument gradually was withdrawn until the water ceased to flow. Previous cystoscopic examination had determined the exact nature of the obstruction. If it was a contracture of the neck of the bladder the slot of the instrument was brought out in the midline below. The eye-piece of the instrument was lightly elevated, the tube was evacuated and dried with a cotton pledget, and a working element carrying the cautery blade was passed through the sheath of the instrument until it engaged the obstruction. The current was then turned on, and by a rotary motion the obstructing band was removed with the punch. In cases of urethral valves, which are always lateral, the instrument was inserted in the same manner, but the slot of the instrument was pressed toward the side from which the operator expected to remove a central section from the band. In none of these patients operated on by the punch method was there any bleeding. A small indwelling catheter was left in place for twenty-four hours. There was no hemorrhage after operation, and in only 1 case was there any febrile reaction. These children tolerated such operations better than adults. No complications developed.

Results were excellent in 13 of the patients. Two patients were improved, and the results were not entirely satisfactory, but further surgical procedures were not authorized by the parents. One patient with pronounced spina bifida, with a thin, delicate valve, showed no improvement after removal of the valve.

*Rupture.*—Scholl<sup>30</sup> stated that the factors usually associated in producing rupture of the bladder are distention, a variable type of trauma and not infrequently an associated mental or alcoholic incompetence. Cases in which rupture of the bladder occurs in association with hypertrophy of the prostate gland are rare, but references to such conditions are occasionally noted in the literature. Rupture in such cases is primarily due to obstruction at the neck of the bladder and secondarily to increased intravesical pressure, plus degenerative changes in the wall of the bladder.

Scholl reported a case of rupture of the bladder resulting from distention of the organ, caused by prostatic obstruction. Patients with traumatic rupture of the bladder generally have severe pain in the lower part of the abdomen at the time of injury. This pain is continuous and associated with vesical tenesmus, and usually the patient is in moderate shock. The symptoms in cases of spontaneous rupture differ only slightly from those in cases in which rupture is caused by trauma. Spontaneous rupture of the bladder is more likely to occur among elderly patients with a history of involvement of the bladder of long standing.

The treatment in both the intraperitoneal and the extraperitoneal type of rupture is usually immediate operation. This condition is a surgical emergency, and delay, particularly when rupture into the peritoneal cavity has occurred, is as dangerous as in the case of any other acute abdominal lesion. When the tear has been through the peritoneum, the abdomen is opened, the bulk of the fluid is withdrawn by suction and the rent in the bladder is closed. Both the peritoneal cavity and the bladder are then adequately drained. In the extraperitoneal type of rupture the main procedure is drainage of the bladder, together with drainage of any perivesical pockets or areas of extravasation. Usually patients with rupture of the bladder are in poor general condition, and rapid, accurate operation is necessary. In the early days of surgery, almost all patients with rupture of the bladder died. The abdomen was not opened without the possibility of peritonitis occurring; consequently there are many patients who were not treated by operation. The associated lesions and complications took their toll, and rupture of the bladder was a serious condition. The present mortality, although still high, is mainly due to the tremendous shock and the coincidental lesions, conditions placing the patient beyond help when first seen. In only a small percentage of cases is the high mortality now due to delayed or unskilful procedures. In cases in which there are no complications, when operation is early the prognosis for both intraperitoneal and extraperitoneal rupture of the bladder should be favorable.

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30. Scholl, A. J.: Rupture of the Urinary Bladder Associated with Prostatic Hypertrophy. *J. A. M. A.* 106:701-704 (Feb. 29) 1936.

*Syphilis.*—Finestone<sup>31</sup> presented an analysis of 158 cases of syphilis of the bladder. There is a scarcity of data in the reported cases, which were neither thoroughly studied nor followed and adequately controlled. Only 8 investigators subjected the lesions to microscopic study. Only 1 investigator discovered the typical histopathologic picture of the disease. It was claimed that 2 investigators found specific histopathologic changes, but the cases were not reported in detail. The 5 other investigators gave descriptions of nonspecific inflammation. Two cases, 1 of which revealed all of the diagnostic criteria used in most of the cases, were described in detail; this demonstrates the pitfalls which are encountered in the presence of disease of the bladder and concomitant syphilis.

*Disturbances of Innervation.*—By means of an air-water manometer and recording tambour, Lewis, Langworthy and Dees<sup>32</sup> made graphic records of the behavior of the detrusor muscle during filling of the bladder. The muscle of the bladder characteristically responds to the stimuli of stretching, and significant information can be obtained by observing and recording waves of contraction of the bladder. Patients who had either bilateral or unilateral injuries of the pyramidal tract or had lesions of motor tracts in the spinal cord were studied. With release from cortical control, the "stretch reflex" is hyperactive. The bladder empties precipitously with a small volume of fluid. When the motor pathways from the midbrain are injured bilaterally along with the corticospinal tracts, the waves of contraction of the bladder are frequent but of small amplitude. They are ineffective in emptying the bladder. A study of contraction waves of the muscle during filling is of aid in forming an opinion of the efficiency of a bladder with injured innervation.

Langworthy and Dees<sup>33</sup> presented records of activity of the bladder in 4 cases of spina bifida. The neurologic involvement in each of the patients was of different degree. It is possible to distinguish predominant involvement of the posterior or sensory sacral roots from that of the anterior or motor roots. The importance of studying waves of vesical contraction is stressed. They may occur spontaneously and rhythmically or in response to sudden stretch of the muscle. If the waves are capable of summation into a strong, tetanic contraction, the bladder is emptied efficiently.

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31. Finestone, E. O.: Syphilis of the Bladder, Surg., Gynec. & Obst. **62**: 93-113 (Jan.) 1936.

32. Lewis, L. G.; Langworthy, O. R., and Dees, J. E.: Bladder Abnormalities Due to Injury of Motor Pathways in the Nervous System, J. A. M. A. **105**:2126-2131 (Dec. 28) 1935.

33. Langworthy, O. R., and Dees, J. E.: A Study of Bladder Disturbances in Spina Bifida, J. Urol. **35**:213-226 (Feb.) 1936.

*Closure of Incisions.*—Davis<sup>34</sup> stated that quicker and more satisfactory healing of suprapubic incisions of the bladder may be obtained by diverting the drainage of urine from the main operative incision in the wall of the abdomen and by allowing the incision to heal by primary intention. The technic employed was a modification of the Pfannenstiel incision. The incision was made in the usual way, except that it was from 4 to 4.5 cm. above the upper border of the symphysis. This required care to avoid injuring the peritoneum but did not interfere with the exposure or incision of the bladder. A mushroom drain of any type desired may be sutured into the bladder. The bladder was then protected by a finger in the prevesical space, and a stab wound was made from the outside through the middle of either rectus muscle and half way between the incision and the symphysis. A large curved clamp was passed through this stab wound, and with it the drainage tube, a Dakin tube, and a cigaret drain were drawn out together through the wound. The incision was then tightly closed in layers. Suturing of the rectus muscles closed the incision completely from the prevesical space.

The sinuses produced by this method tend to contract rapidly, probably because they are closely surrounded by the tissue of the rectus muscles. For this reason leakage of urine around the tube was rare, and the fistula tended to close quickly after the tube was removed. The tube can be replaced if necessary, preferably with a Malecot drain. The original tube may be of any size, but the aforementioned characteristics of the fistula make this method of operating less desirable in cases in which extensive intravesical procedures may become necessary after operation. It is suitable, however, for cystostomy, lithotomy and other procedures involving less risk of hemorrhage.

*Displacement.*—Hepler<sup>35</sup> reported 5 cases of displacement of the bladder secondary to suppurative arthritis of the hip and osteomyelitis of the pelvic bones in children and described an operation for impending perforation.

This displacement is caused by the intrusion into the pelvis of an enormous involucreum. The bladder becomes attached to the involucreum and is displaced laterally. This displacement is caused not by an intrapelvic abscess, but by a hard bony mass. Perforation of the bladder is threatened or impending by sequestrums, with the production of an

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34. Davis, D. M.: A New Method of Closing Suprapubic Bladder Incisions, with Remarks on the Prevention and Treatment of Infection in Urinary Wounds, *J. Urol.* **35**:41-48 (Jan.) 1936.

35. Hepler, A. B.: Bladder Displacement Secondary to Suppurative Arthritis of the Hip and Osteomyelitis of the Pelvic Bones in Children: Operation for Impending Perforation, *J. Urol.* **35**:32-40 (Jan.) 1936.

osteovesical fistula. When perforation occurs it is chronic or subacute, with the entire side of the bladder firmly adherent to the involucrum, so that there is no urinary extravasation or leakage.

This condition has not been described before, possibly because of the absence of signs and symptoms referable to the urinary tract. Even in the 2 cases in which perforation was present, there were no subjective symptoms and an examination was made simply because of a persistent pyuria.

The absence of urinary signs or symptoms is no indication that displacement of the bladder is not present. Therefore, cystograms should be made as a routine measure.

If displacement is present, then the operation described should be performed, first to prevent perforation of the bladder, and second, of equal importance, to bring about a more rapid subsidence of the osteomyelitis by sequestrectomy, curettage and drainage of the sinuses through the pelvis. After months of the usual orthopedic treatment, the 3 patients on whom operation was performed improved rapidly and were discharged in a comparatively short time.

Once corrected, this condition does not tend to recur provided the osteomyelitic region is adequately drained.

*(To be concluded.)*

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